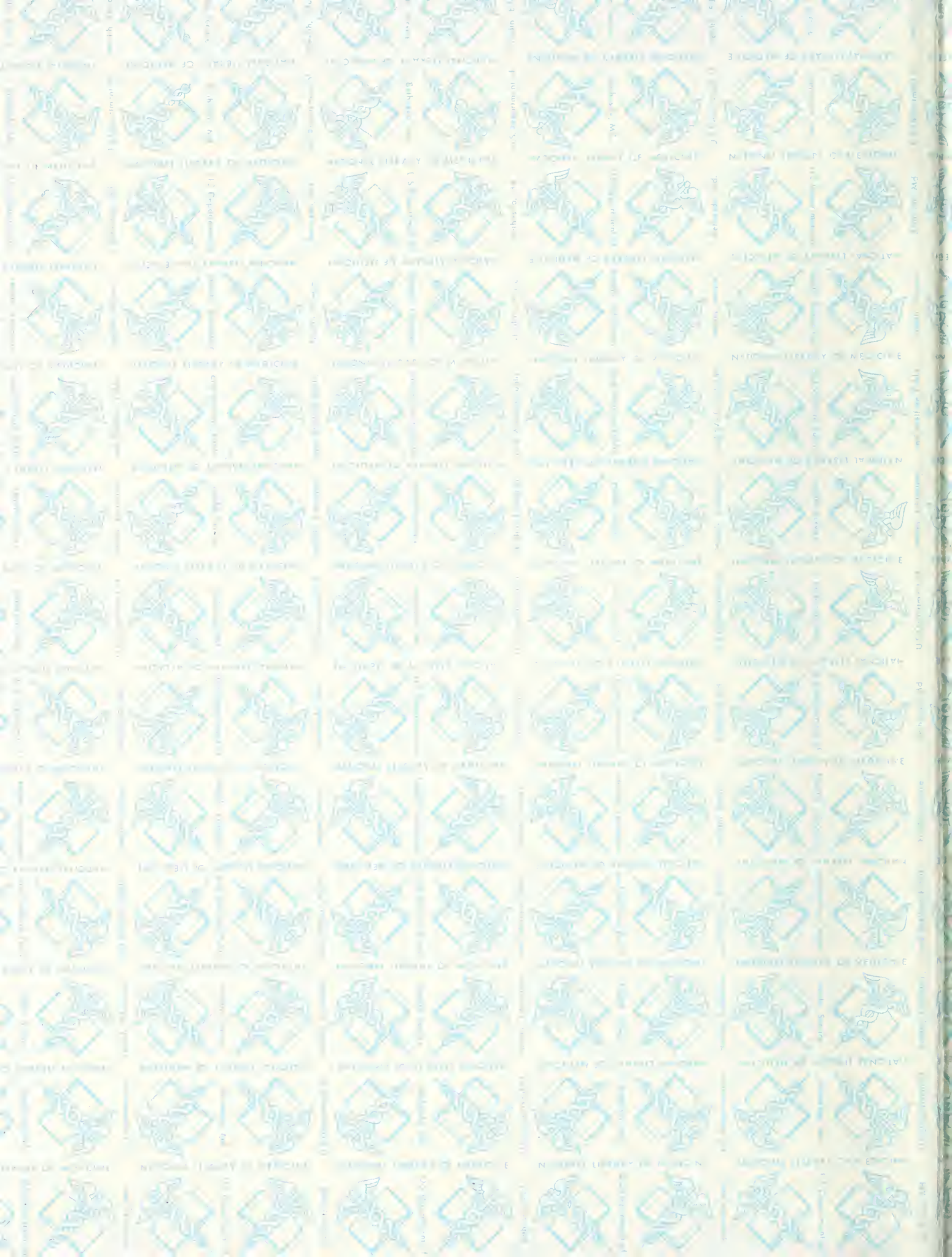


SPEECHES, ARTICLES, AND
SELECTED PAPERS

Donald S. Fredrickson, M. D.

1975-1981

Volume 1



*National Institutes of Health (U.S.)
Office of the Director*

SPEECHES, ARTICLES, AND SELECTED PAPERS

By
Donald S. Fredrickson, M.D.

1975-1981

Volume 1 (of 3)
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THE PURPOSES OF THE NATIONAL INSTITUTES OF HEALTH*

1. On the Translation Gap

Introduction

History will record at least two occasions when medical care was on trial in America in the twentieth century. The first time was on a charge brought by Flexner and his supporters in about 1910. Guilt was pronounced for proliferation of quackery and the defendant was remanded to the custody of biomedical science for reform. The probationer and trustee prospered in this new relationship. Together they brought off a revolution in new knowledge of biology and its application to disease that had a profound effect upon the life and happiness of humans throughout the world.

Some 50 years later, it was a shock to both when medical care was publicly indicted again. It was alleged that the fruits of the revolution were being distributed unequally among the populace and with indifference to mounting strain upon the public purse. The principal accusations on this occasion arose from the Federal Government. During the years following the second World War, the Government had become the largest single purchaser of medical care. The role of Government had also changed toward assuming a responsibility for guaranteeing health as one of the civil rights. In the intervening years, a change had come about, too, in the definition of health. More was implied than simply the diagnosis and treatment of specific diseases. Health had come to mean no less than some regulating of the number and fitness of children born into a society, a thorough understanding and improvement of the physical and social environment in which people live and work, the helping of each person to know something of his genetic constitution and how he might best modify his lifestyle to adapt to his environment and avoid disease, the restoring of function and adaptation when they fail prematurely, the easing of the discomfort of the incurably ill and the aged, and the assuring that when life must end, it does so with dignity. As the Government prepared itself for a not distant time when it might become the fiduciary through which all such multiple services would be purchased, the substance of health care also came under scrutiny. Questions were asked about the balances between costs and benefits of what the physicians and hospitals provided. Some also were stressing statistics that showed factors other than medical care were more important determinants of mortality in the ages between 1 and 40.

Future historians will also note that by the three-quarter century mark, a perceptible shift was occurring in the frame of reference by which human values are assessed. In a society grown increasingly technological and rapidly changing many of its social norms, reactions were occurring to all kinds of previously privileged institutions and professions. Threats to individual privacy and dignity were now perceived in what man was doing in the name of mankind.

*Written in July 1975 as one of a series on NIH, this paper was widely distributed to Bureau, Institute, and Division directors and others. It contains the first suggestion of what later became the NIH Consensus Development Conferences. Only two of the essays proposed in the text have been prepared.

Thus, that complex human endeavor known as biomedical research found itself, in 1975, at least tangential to the paths of two powerful and somewhat uncertain movements for reform. One was economic, and had to do with the costs of applying the products of research to improve the public health. The other was an ethical movement that saw some of the processes and some of the products of research as creating social choices that could no longer be left to the experts. Science, nurtured on an internal ethic that insists upon quantitative and reproducible proofs for the solving of problems, was also accused of withdrawing from many of the "impossible decisions." The legislatures and the courts, more experienced at coming to conclusions where underlying premises were subject to eternal change, were less hesitant. There was a rapid proliferation of administrative laws, which simultaneously challenged many institutions to respond to newer perceptions of public need and threatened to impinge upon the traditional freedoms of those institutions.

So much for a brief statement of contemporary conditions. The questions we must ask ourselves is what does all this imply for the National Institutes of Health? What are its present purposes? We cannot be unmindful that the pre-eminence of this institution is such that any re-articulating of our purposes must have important effects upon the world of biomedical research. Let us not deter from addressing our current problems, however, while it is possible for us to have important influence on their solutions.

There are many compendia of unsolved issues concerning biomedical research. Indeed, there is a Presidential Panel in the midst of more than a year's deliberation of them. We are prepared to assist them in every way we can. We cannot wait upon their recommendations before taking many necessary actions ourselves. My own perceptions of where action is particularly needed include (1) realistic assessment of the boundaries between biomedical research and health care, with particular attention to necessary extensions of the research continuum in the direction of clinical investigation without imperiling the research that must precede it; (2) a coming to grips with the elusive definitions of demonstration and control exercises which, for NIH, should mainly be special classes of clinical trials; (3) the corollary issue of dissemination of research results, a problem of communication and coordination among scientists and between their community and the health practitioners, as well as one of educating the public; (4) health maintenance of the biomedical research apparatus, including credible assessment of Federal subsidy of its manpower needs; (5) the decision processes whereby we settle our allocations, including the form and quality of societal involvement; (6) the future organization of the NIH such that need and opportunity for discovery remain matched; and (7) the critical need for modernization of NIH campus facilities and a possible requirement for adjusting intramural research modes after wise projection of future requirements..

The remainder of this essay addresses mainly the first issue.

The Biomedical Research Continuum.

The purpose of biomedical research is improvement in the well-being of man through greater understanding of the nature of life. It is a continuing quest for knowledge, an enterprise that depends more upon disciplined imagination and hard work than it does upon single creative strokes of genius or serendipity. Whether master, assistant, or apprentice, the people involved now days are highly specialized professionals; a role for amateurs or dilettantes has practically vanished.

Biomedical research is rooted in biology, the discipline concerned with the fundamental processes shared by living things. The thrust of such research is toward reduction of these essential functions to chemical and physical terms and then to re-order this information into rules and patterns that explain the differences between the living and the inert. Often called "basic research," the discovery of cycles that transmute energy, regulate metabolism, or the intricate mechanisms for transmitting and transcribing the genetic code is also "applied research" in the sense that one transfers to complex systems the techniques and the descriptors of other sciences. The search for knowledge involves successive amalgamation of new facts with old ones and continuing resynthesis of the whole. Although, at any one time, the applicability of much of such fundamental research necessarily remains obscure, there is a constant desire that any discovery shall have some practical importance. Those whose lives are spent working upon bacteria or plants are no less conscious of this than those who work on human problems.

Perhaps nothing about life that has been learned so far is more important than the revelation that the biological processes which determine the growth of an organism from conception, that program its eventual death and sustain life in the interim, appear to be so remarkably similar from bacteria to man. It detracts nothing from the splendor of the human consciousness to recognize that myriad lower forms of life have much of the same biochemistry as does man and that they have perhaps retained superior features of certain common systems. This limited divergence of fundamental processes is the strength and the rationale for the concept of biomedical research as a continuum.

There is very little that is learned about any form of life that is not ultimately relevant to man. And much of that still vast unknown that is man must still be learned through study of the many other species upon the earth.

There are undoubtedly some in biology who wish that the medical half of biomedical research, with its pressing social issues, could exist separately. But the marriage of biology to medicine is no more dissoluble than the marriage of biomedical research to health care. Understandably there is a practical limit to the public desire to be the patron of biology or biomedical research as solitary entities. There are more compelling intellectual reasons for these unions. Medicine has frequently been a tutor of biology. The steadily increasing capacity for reduction of certain diseases to molecular terms steadily enhances

this cross-fertilization. There are now numerous examples of enzymes, of new functions for other proteins, and of metabolic pathways that were unsuspected or could not be proved in studies limited to normal organisms. The resulting surge in biomedical knowledge acquired in the past 30 years will stand as one of the greatest periods in the history of science and probably of all human endeavor.

Clinical Investigation. In this regard, it is worth noting a singular national contribution to this world-wide jump in biomedical knowledge. Although the generous level of investment in all phases of research contributed by America has been an essential catalyst, I have reference to our supremacy in the coupling of medicine and biology.

In no other country of the world has clinical investigation yet risen to the level of the art obtaining in America. And it was here in our own NIH Clinical Center that the present standard for the co-engagement of biology and medicine was set and propogated to the medical schools in both America and abroad. In a 10-year period from 1953, Bethesda became what Dessau was once to architecture, what Vienna was to music, and Paris to cuisine. It happened here for a mixture of reasons that had to do with the sudden collection of a large and critical mass from that small fraction of the graduates of the medical schools who choose research as a career. Freed of all or most of the burden of clinical service, they were distributed among many of the best at that time engaged in the laboratory sciences. I can recall in quite personal terms how the exposure to so broad an array of fundamental research, provided by critical and highly accessible tutors, put an indelible optimism over the power of the scientific method in approaching the mysteries of the sick.

Clinical investigation, a hybrid science, is not an easy business. The approaches one learns in the laboratory become severely constrained when human beings participate as the experimental subjects. The welfare of the subject is paramount and his interests may not be displaced for the good of society or allowed to be confused with the ambitions or the curiosity of the scientist. It is also not possible for the physician to restrict himself to disinterested observation. He has to be able to convey a conviction in miracles while silently believing in the laws of probability. And he is bound in today's conventions to assure himself and his subject of the potential benefit to the latter of whatever is proposed.

Nevertheless, a good deal of clinical investigation is not directly concerned with treatment or prevention and some of the best work of this genre has been conducted with an air of therapeutic nihilism. The most trying phase of biomedical research involves proving that an intervention is safe, practical, and efficacious. The more chronic the disease, the more obscure its pathophysiology and homogeneity, and the more its progress becomes. The ultimate effort is the randomized clinical trial (RCT), a prospective test of an hypothesis under the most objective ciricumstances in which both observer and subject are blinded. Sometimes these exercises seem to require the proportions and the zeal of a Crusade, as they move into terrain that is shadowed by the preconceptions of those who would heal or those who would be healed, by

the self-interests of vendors, and especially by the complexity of the human organism, which has evolved over millenia a set of checks and balances designed to nullify the effects of interventions.

The large-scale clinical trials are not popular with many life scientists, who see them as a potential drain for the resources supporting all biomedical research. They have up to now also not been used widely as models of scientific medicine by the academicians who teach medical students. This negative image has been largely earned; there have been many examples in the past of ill-conceived, premature experiments by which equivocal answers have been purchased at great cost. Some of the mistakes were faults in experimental design; we have been instructed by these. Some of the errors were due to the tacit withdrawal from the decision-making by experts who knew better but disdained to argue. We have been instructed by this, too, in latter-day criticism of the methods by which science arrives at its priorities. All in all, I should say, however, that the last 3 decades have seen considerable and progressive growth in our knowledge of how to conduct clinical trials; in the selection of population size and endpoints; in use of placebos and the double-blind; in evaluating costs against the probability of obtaining a correct answer, or any answer at all; and in becoming masters of the awesome power of data processing for epidemiologic purposes.

Uncertain Interventions.

These new arts have arrived in the nick of time, for we are being called upon to participate in a shakedown of the substance of medical care, an activity from which biomedical research cannot conceivably withdraw.

The current interest in quality and cost-effectiveness of health care practices has risen as much within the health professions as outside of them. Realization has not suddenly dawned that the substance of medical care has a large empirical component. It has long been an established part of the healing process to take actions without proven validity provided they did not seem to be more harmful than doing nothing. And provided the cost could be borne. It is in the matter of cost that tolerance of such practices has mainly collapsed; but there is also the influence of a steadily growing skepticism and social awareness among the younger generations of physicians and other health professionals.

There are three major categories of health care interventions affected by heightened consciousness of cost-effectiveness and efficacy. First are tests and interventions already widely disseminated and accepted in medical practice. These are targets of "quality assurance" programs now established by legislation yet in the first stages of implementation. As some of our sister agencies in the Federal Government begin to cope with this challenge and the voluntary health sector looks on with trepidation, there emerge several alternatives.

One possibility which has some proponents among the aficionados of PSRO is to embark on an inventory of the vast storehouse of health practices, collect and sift the evidence bearing on their efficacy and cost-benefit with the aim of an eventual codification of all the things physicians

can do and hospitals may permit to be done, and for which payment will be made. An interesting question here concerns who would constitute the "boards of clearance" and appeal for so tedious and difficult a process.

A more practical alternative is to achieve by diligent effort a lowering of the threshold of skepticism throughout both the biomedical research and health care systems and acceptance of a collective responsibility for the cost-effectiveness and efficacy of interventions. With appropriate leadership and modest organizational changes, the natural decay of doubtful practices could be accelerated, leaving a smaller residue to be the subjects of formal testing.

A third alternative is to do nothing but assume that the system will correct itself least expensively in a laissez-faire fashion. Unfortunately this argument is usually phrased, "let us do nothing to interfere with the practice of medicine," a reflexive defense against all forms of external interference. Its credibility has suffered irremediable damage.

I favor the second alternative and believe it is in our greatest interest to determine what more we should do to bring it about.

The second group of interventions relate to translations of research into clinical care that have not yet entered the general substance of health care. Here again there are several options. We might go the British route, which increasingly is to require randomized clinical trial (ideally at least two) of every major new intervention before it enters the list of acceptable billings. As you know, England has not restricted this examination to esoterica. Archie Cochran, their best-known proponent of the RCT, is particularly proud of the evidence accumulated indicating that British males with myocardial infarction do just as well at home as in the coronary care unit provided there is a solicitous wife or mistress in the household. And doubtless there are more controversial surprises in store.

A second option is to stop short of a stringent requirement, yet enhance certain qualities of the existing system. It already includes some potent regulatory activities of the FDA, which have recently added devices to their prior domain over drugs and biologics. It's not in the public interest for NIH to usurp any of the hegemony of FDA in such regulations. Indeed, it is necessary for us to act as the sponsor of certain INDs for interventions not of interest to commercial vendors. Our responsibility, however, is to understand more completely and to improve the somewhat informal system whereby consensus is reached concerning the validity of the interventions arising from our research. Are there better linkages between the institutions, centers, and other clusters of experts we subsidize and the editorial and collegial processes whereby discoveries are deemed proper for general application? How can we extend the continuum of biomedical research across preceivable gaps in translation?

Let me briefly mention a third and special class of the progeny of research. This is the high cost technology ("half-way technology" in Thomas' felicitous term) that may add something to the length of life by

tertiary care yet jeopardize other research directed toward prevention or other long-range solutions. Many accusations have been made against modern science for failing to consider the consequences of embarking upon development of such technology. This includes umbrage at the manner in which the interested public seems to have been excluded from the debate. You will recognize this last as a special case of a more general problem. Program leaders today, however, need to develop an aptitude for anticipation of costly weeds which their developmental activities may be sowing in the garden of technology--an aptitude which was not necessary a decade or two ago. The issue is delicate and far from simple, for it borders on infringement of inquiry and interference with the natural flow of research translations. We will need to devote future time to exploration of this part of priority selection.

The Clinical Trial.

The first two categories of problems within or at the edge of the substance of health care--in our case, mainly medical care--bear direct relationship to the clinical trial as a research instrument. These were an issue in the 1975 Analytical Agenda for NIH and became the subject of a report by NIH scientists entitled "The NIH Clinical Trial Issue Paper," a summary and detailed analysis of the support of clinical trials by the NIH. Let us briefly examine what this document has to say on this key issue for NIH. We can begin with the note that it is a commendable report, thoughtfully written, and a useful site for launching further agreement concerning definitions needed for subsequent inventories of clinical trials and improvement in handling the multiple problems they present.

NIH Definition of Clinical Trials. In the forementioned report a clinical trial is defined as a . . . research activity undertaken to define prospectively the effect or value of prophylactic or diagnostic or therapeutic agents, devices, regimens, procedures, etc., as applied to human subjects. In the tabular data supplied we learn that four institutes supported a total number of major trials that exceeded \$114 M in 1974, and that the obligations for clinical trials grew perspective faster than total clinical research obligations or total research obligations during the 3-year period from 1971. An obvious problem with this information is the uncertainty as to just what is meant by "major clinical trials." Has a useful taxonomy been developed whereby such research can be analyzed and displayed for a variety of purposes? We need to know, for example, how many of these exercises were full-fledged randomized clinical trials, what kind of control populations were involved, what were the numbers of subjects and other features that might instruct us in the many generic issues common to this kind of experimentation. The report makes oblique reference to the separation of clinical trials into phases one through four. These appear to be the definitions promulgated by FDA, a breakdown which has limited utility for our purposes. An important task, therefore, which needs early attention, is the development of a more useful set of definitions of clinical trials. All of our B/I/Ds should use a common language in this regard.

The Desirable Level of NIH Support for Clinical Trials. The NIH Committee correctly concluded that there exists no useful analytical approach to determine the appropriate level of NIH investment in the support of clinical trials. First, there is the definitional problem already alluded to. Its solution may speed a more critically needed opinion as to which kinds of clinical testing NIH should best conduct or support, or more appropriately, leave to other agencies within HEW, the Veteran's Administration, or the pharmaceutical industry and other privately supported groups. No doubt the level of NIH activity, as well as the intensity of involvement of all the alternative groups, will also depend upon the influence that we can bring to bear on the philosophy of how problems of "quality assurance" and cost-effectiveness of interventions should be faced. There must continue to be a high degree of selectivity in choosing questions to be solved by clinical trials. An important premise is that the greater the knowledge base supporting a trial, the more likely it is to succeed. A corollary for NIH is that the more a given trial would appear to benefit from the participation of major contributors to its underlying knowledge base, the more suitable it is for NIH to conduct it. For the kinds of clinical trials that we come to judge not appropriate for this Agency, we have another obligation. This is to see that the need is met elsewhere and thus lend our encouragement to the strengthening of other agencies for the task.

Clinical Trial Methodology. I support the recommendation that NIH should underwrite more studies designed to examine questions of clinical trial methodology. The experience acquired in the past several decades has exposed certain matters which are ready for refinement and incorporation into useful algorithms. These include issues of evidence and proof, ways to assemble and establish collective doubt sufficient for commencement of a trial, the continuing monitoring of safety and adherence design, the deciding of when to stop, and the handling of ethical problems. It should be pointed out that, in study of clinical trials, the experiments are the trials themselves, and that a major effort needs to be made to elevate both the art and the status of critique of them. Thus there may be accumulated a body of well-studied and reasonably codified case experience from which important lessons can be disseminated to all concerned. Not the least of the tasks to be done better is the informing of the public of the complex nature of clinical trials, their many limitations, and extraordinary potential for eliminating waste of public resources.

Funding of Clinical Trials. A precipitous rise in the number of clinical trials, which would attend sudden enthusiasm for re-examination of the substance of already existing medical care, will create serious problems of funding. It is an urgent matter that NIH and HEW consider carefully how recommendations and proposals may be developed leading to amortization of the costs of certain trials through national health insurance. This includes a study of the indemnification of adverse accidental effects of clinical studies. Emphasis must be given to the prospective savings in the cost of health care that can be realized by appropriate clinical trials. The Administration and the Congress need both information and encouragement to act upon it. - The budgets for research and other health activities could become seriously depleted by an orgy of end stage technology testing.

Dissemination of Results of Clinical Trials. This is a special subset of the larger problem of dissemination of research results in general. The NIH is now under increasing Congressional pressure to take action in this regard. I have already made reference to a need for a scholarly analysis of the decision processes whereby the results of research are validated and disseminated into practice. It is but one of several stages of communication, and the overall issue will be dealt with separately in further discussions of desirable improvements in the contemporary processes governed by NIH support.

Organization. The NIH Committee recommends the establishment of an NIH-wide Committee, composed of representatives from B/I/Ds, to share information on clinical trials that are planned or in progress and to provide some broad policy recommendations to the Director, NIH. Its success would be judged by the mechanisms it creates for providing information about when a trial of a certain size or character is launched, the criteria employed in the establishment of the experiment, its progress and outcome, and finally the all important exercise of critique. I favor establishment of such a coordinating group when the small NIH task force, now grappling with the information matrix for a 1975 inventory of clinical trials, has completed its work next month. The NIH Committee further recommends the establishment of an interagency coordinating committee composed of all Federal organizations involved in the support and conduct of clinical trials or the assessment and application of their results. Here again this is a commendable objective in terms of providing an enhanced degree of information exchange. It would appear that the problems faced by such a committee are a multiple of those anticipated for the organization proposed for NIH itself, although a larger organization will be required and NIH will cooperate closely with its sister agencies having similar responsibilities. I think it is wisest for us to develop a format for the intra-NIH coordination group which might provide a base for establishing further interagency cooperation. We must move swiftly so that the efforts of task forces extending across the health agencies will not be a wasteful or idle exercise.

Summary.

The need for closing the translation gap that exists between biomedical research and the effective application of its discoveries is a major issue requiring the attention of the National Institutes of Health. An element of urgency is derived from a national determination, largely Government directed, to increase the cost-effectiveness and efficacy of health care. The importance of clinical trials to NIH is several-fold. They provoke a reaffirmation of the necessity of the union of biological and medical research, while simultaneously they raise a question of how far the Agency's resources can be deployed in matters of medical practice before its principal mission of discovery is imperiled. Thus, they are one element in the complex question of where the appropriate boundaries of NIH activities lie. Clinical trials also force us to consider how well we understand the apparatus that is supposed to provide for orderly translation of discoveries into the substance of medical care. The processes of validation and continuing

re-evaluation do not always operate smoothly or even serially. The loose confederation of diverse talents and interests involved need better articulation. Perhaps the essential first step is the more formal recognition of collective responsibility for any gaps in translation that persist. If this is achieved, we may expect some solutions to flow forth, given the creativity inherent in the community at interest. In the present paper some suggestions have been made toward this objective. They are intended to stimulate further discussion among those most concerned with the purposes of NIH.

Donald S. Fredrickson, M.D.

ANIMAL WELFARE ACT AMENDMENTS OF 1975

HEARINGS
BEFORE THE
SUBCOMMITTEE ON LIVESTOCK AND GRAINS
OF THE
COMMITTEE ON AGRICULTURE
HOUSE OF REPRESENTATIVES
NINETY-FOURTH CONGRESS
FIRST SESSION
ON
H.R. 5808
and Related Bills

SEPTEMBER 9 AND 10, 1975

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ANIMAL WELFARE ACT AMENDMENTS OF 1975

TUESDAY, SEPTEMBER 9, 1975

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON LIVESTOCK AND GRAINS
OF THE COMMITTEE ON AGRICULTURE,
Washington, D.C.

The subcommittee met at 2 p.m., pursuant to notice, in room 1301, Longworth House Office Building, Hon. W. R. Poage (chairman of the subcommittee) presiding.

Present: Representatives Poage, Bergland, Weaver, Harkin, High-tower, Bedell, English, Wampler, and Sebelius.

Also present: Robert M. Bor, counsel; Hyde Murray, counsel; John Hogan, associate counsel; John Baize, staff consultant, Subcommittee on Livestock and Grains; and Margo Shildkret, staff assistant.

Mr. POAGE. The subcommittee will come to order. We are here today to deal with H.R. 5808 which deals with the Animal Welfare Act.

[The bill H.R. 5808 and the reports from the U.S. Department of Agriculture, U.S. Postal Service, and the Interstate Commerce Commission follow:]

(1)

Thank you, Mr. Chairman. We will be pleased to respond to any questions you may have.

[The exhibits referred to are held in the subcommittee file.]

Mr. POAGE. Thank you very much. We appreciate that statement.

Our next witness is Dr. Donald S. Fredrickson.

[The prepared statement of Dr. Fredrickson follows:]

STATEMENT BY DONALD S. FREDRICKSON, M.D., DIRECTOR,
NATIONAL INSTITUTES OF HEALTH

Mr. Chairman and Members of the Committee: I am pleased to be here today to discuss the important issue of humane treatment and care of animals used in biomedical research. The National Institutes of Health and the Department of Health, Education, and Welfare are appreciative of this Subcommittee's support for our continuing efforts to promote animal welfare, and we share with you the concern that all animals used in research receive proper handling and care.

As an agency changed by the Congress with responsibility for the conduct and support of biomedical research in order to improve the health of the American people, the National Institutes of Health has a special concern with animal care standards. The use of animals in research is an absolutely essential part of our efforts to fulfill this responsibility.

The final determination of the effectiveness of a treatment for cancer, or any other disease, can only be known when actual tests are conducted on human patients. When scientists have developed a new drug or surgical procedure which they feel might be useful, the potential hazards or adverse effects of such untried substances or procedures cannot always be predicted. Thus, in spite of large, and to some extent unknown, physiological differences between human beings and animals, scientists have found that in many cases the basic life processes of many animals are sufficiently similar to those of man so that by choosing an appropriate animal model one may reach useful conclusions concerning the way drugs, surgery, or other therapy work without endangering human life.

It is because we have at best only partial answers to questions about man's complex biology that we are conducting research. Although we are doing all we can to refine other research procedures based on our ever-increasing source of knowledge, the use of laboratory animals remains one of our most important and vital resources in the fight against disease and illness.

Let me emphasize also that, because animals are so vital to our research enterprise, we recognize our moral obligation to make every effort possible to see to it that research animals are well cared for and treated humanely. Reinforcing this moral obligation is the practical consideration that only through the use of healthy laboratory animals can scientists obtain the accurate and reliable research results necessary to further knowledge and the progress of medical science.

Today, hundreds of thousands of people owe their health and their lives to medical research. Most of this research required using laboratory animals. The list of those who have benefited includes burn victims, those suffering from shock and serious injury, and victims of cancer. The giant strides in the conquest of poliomyelitis, for example, would have been impossible without the use of laboratory animals. Highly complex surgical procedures, such as the "blue baby" operations, artery and organ transplantations, and refinements in orthopedic surgery were based on experiments on animals. Every man, woman, and child who has had a vaccination; all who take prescription drugs for high blood pressure and other chronic illnesses; almost everyone who has ever received treatment for a serious medical problem owes such treatment to the tremendous advances in biomedical research which in some measure was based on the use of laboratory animals. And, of course, animals themselves have benefited from this research, since the veterinary practitioner applies the results of the same finding when treating pets and livestock.

In the United States, millions of animals are used in research annually. The National Institutes of Health alone uses approximately three-quarters of a million laboratory animals per year in its Bethesda laboratories and five million in the drug screening programs of the Division of Cancer Treatment of the National Cancer Institute.

Because healthy, well cared for animals are so important to our medical research programs, within the past few years we have taken a number of steps to promote the welfare of laboratory animals. In 1971, the National Institutes of Health issued a policy statement regarding the care and treatment of animals used in all of its sponsored research programs and activities. In 1973, the policy was strengthened and broadened to apply to the entire Department of Health, Education, and Welfare. It requires that institutions receiving funds from the Department submit in writing an assurance that they have established a mechanism for evaluating their animal care programs consistent with the standards established by the Animal Welfare Act (P.L. 89-544 as amended by P.L. 91-579) and the "Guide for the Care and Use of Laboratory Animals" [DHEW Publication No. (NIH) 74-23] written by the National Academy of Sciences—National Research Council. The policy also directs review groups to note any improper or inappropriate use of animals and requires that these issues be resolved before a grant or contract can be awarded.

In addition to taking steps to ensure that the present law regarding standards of animal care is carried out, the NIH also has an active animal resources program designed to increase and improve laboratory animal facilities and resources. Projects supported through this program include the development and maintenance of colonies of special research animals, assisting institutions in complying with statutory and policy requirements for care of laboratory animals, improvement of health care and examination of environmental requirements of laboratory animals, and the gathering and dissemination of information on research animals.

Since the passage of the Animal Welfare Act of 1970 (P.L. 91-579), the National Institutes of Health has invested over \$10 million in helping its grantees achieve the required standards of animal care. In addition, nearly \$2 million has been invested in training of people for animal resource programs. For our intramural research program in Bethesda, a new primate building incorporating larger, improved cages has been constructed at a cost of \$1.2 million.

I can assure you, Mr. Chairman, that we recognize our obligation to ensure that animals are used only where they are essential, and that those used are treated humanely not only in our own intramural program but throughout the biomedical research community.

Turning now to H.R. 3508, Mr. Chairman, the Department of Health, Education, and Welfare generally defers to the U.S. Department of Agriculture because it has the responsibility and expertise in the administration of animal transportation laws. However, we would like to speak to one particular feature of H.R. 3508 that is of concern to us. Section 10 would require that all animals delivered to, or received by, an intermediate handler or common carrier be accompanied by a veterinarian's certificate of health and soundness. We understand this is intended to eliminate a major problem with the shipment of unhealthy or unsound dogs and cats for the pet trade. As now written, the bill would include literally millions of mice, rats, and other commonly used laboratory animals bred under carefully controlled conditions and shipped by common carrier for use in research. A veterinarian's certificate would be a needless impediment to this commerce, and such a requirement could disrupt the flow of laboratory animals that are so vital to our continuing biomedical research effort.

We feel that much has been accomplished in the area of animal welfare. The existing legislation, administered by the USDA, has enhanced our efforts to achieve the goal of assuring that all animals be well cared for. The NIH and DHEW have worked closely with the USDA over the years in promulgating appropriate regulations and in coordinating efforts to execute the Animal Welfare Act, as amended.

In conclusion, let me assure you that we share the concern expressed by many about the humane treatment of animals. The NIH and DHEW stand willing and ready to work with the USDA and any other agencies concerned with the welfare of animals.

I am happy to have had this opportunity to discuss the efforts of the National Institutes of Health in this important area of concern. I would be pleased to answer any questions you may have.

Dr. FREDRICKSON. Parenthetically, I might add one other point here, Mr. Chairman. On occasion, for research purposes it is necessary to ship animals with certain diseased conditions from one laboratory to

FROM THE OLD TO THE NEW*

Donald S. Fredrickson, M.D.**

In the course of a professional life spent in science and academic medicine, one expects to get involved in several serious flirtations with institutions, a career-marriage in mind. I confess that several years ago the University of Rochester and I had one such "meaningful relationship" for a short time. And coming back to help dedicate a building...in whose unfinished skeleton I have earlier walked, and left some vaporous imaginings of myself in future residence...has special significance for me.

It is, therefore, not as a total stranger, and with particular pleasure that I serve as one representative of the outside world on this happy occasion. I also serve as a willing substitute for David Mathews, the new Secretary of the Department of Health, Education, and Welfare, who would like to have been able to be here himself. I hope later this morning to convey his best wishes to Mr. Marian Folsom, one of Dr. Mathews' most distinguished predecessors as Secretary

*Presented at the Rededication of Strong Memorial Hospital, Rochester, New York October 4, 1975.

**Director, National Institutes of Health

of HEW and a citizen of whom this community must be especially proud.

History will record at least two occasions when medical care was on trial in America in the twentieth century. The first time was on a charge brought by Abraham Flexner and his supporters in about 1910. The charge was proliferation of quackery. The verdict was Guilty. The defendant was remanded to the custody of biomedical science for reform. Together they brought off a revolution in new knowledge of biology and its application to disease that had a profound effect upon the life and happiness of humans throughout the world.

The second indictment occurred some 50 years later. This time the charge is that the fruits of the scientific revolution are being distributed unequally among the populace and with indifference to mounting strain upon the public purse.

Strong Memorial Hospital was born in the aftermath of the first of these trials and has chosen to be re-born in the time of the second. This gives us good reason to examine the past and transpose its lessons into future tense. The exercise becomes especially important if one realizes how central is the role played by the medical schools and their

teaching hospitals in setting the tone of American medical care.

After Flexner had exposed the weaknesses in American medical education, he became chief executive of the Rockefeller-endowed General Education Board. As such he was able to direct millions of dollars into reform of the system.

He considered several university settings and decided that Rochester had the necessary ingredients from which a medical school of the highest character could be built and urged its development as an example for the nation.

Flexner was persuaded by the academic soundness of the University, the competence of its President, Rush Rhees, and the potential for local financial support.

George Eastman, in turn, became persuaded by Flexner and Rhees of the need for and potential of the School of Medicine and Dentistry at Rochester. His gift of \$5 million matched by the General Education Board provided the financial foundation on which to build.

I need not add further mention here of how critical and how wise was the decision made by President Rhees in 1921 to appoint George Whipple as the founding dean.

I personally knew none of his original department heads.

Although having made my scientific career in lipids, I had more than a passing acquaintance with the ether-ethanol mix we used to call "Papa Bloor's Solution," a durable concoction of the first Professor of Biochemistry. The original Chairman of Bacteriology, Stanhope Bayne-Jones, also spent the last two of his many productive years writing and studying at the National Institutes of Health.

The structure we rededicate today carries the unmistakable stamp of George Whipple's insistence that the teaching hospital be integrally a part of the teaching and research activities of the Center. It is significant that Strong Memorial Hospital constituted a department of the new school and that the first faculty member appointed by Dr. Whipple was Dr. Nathaniel W. Faxon as director of the hospital with the status of full professor in the school.

The close relationship of the schools and hospital was not only conceptual and organizational. George Whipple's idea was that the whole establishment should be physically concentrated in one great building.

The timely fiscal intervention by the two daughters of Henry Strong made it possible for the Strong Memorial Hospital to be built as a part of the original plan. More than one hospital was integrated into the Center. For at that time the City of Rochester was about to build a large municipal

hospital on a site which had been selected by its Health Officer, George W. Goler. On learning of the plans for the new medical school, Dr. Goler sacrificed his personal ambition to direct this new facility and proposed that the city should build it alongside Strong Memorial and put its medical services in complete charge of the University of Rochester.

The physical integration of the hospitals into the Center was symbolic of part of the Flexnerian reform in medical education. The other part was the heavy emphasis on a scientific base for what the students and house staff were to be taught in these new quarters.

The Center was to be a sterling example of the new paradigm of scientific medicine soon to be seeded from a few primary sources - Baltimore, Nashville, Rochester - across the nation.

Although America can take special pride in its past contribution to biological knowledge and its adaptation to medicine, biomedical research is not as native as apple pie. The Constitution mentions the promoting of science only in regard to patents. The Declaration of Independence is silent on the subject. During the first 150 years of the Republic, we were mainly passive inheritors of long tradition of inquiry

traceable from Egypt through successive civilizations. The great medical advances of the nineteenth century dealing with respiration and metabolism, the promise of the Roentgen ray, as well as the bacterial causation of disease and the life-saving possibilities of vaccination and asepsis, were gifts to the New World from Western Europe.

Preoccupied with territorial and economic expansion, America rather slowly increased its contributions to basic biomedical knowledge. And during the first half of the twentieth century, Rochester was one among relatively few centers where there was maintained an environment of excellence which could nurture creativity. Before 1945, biomedical research was supported almost entirely by private philanthropy and the limits of this support were depressingly low. The resources to study increasingly complex biological problems were hard to come by.

A dramatic growth of biomedical science in this country came about as a result of the acceptance - after World War II - of public responsibility for its finance.

With the creation and thriving of the NIH, and to a lesser extent, as measured in dollars, of its basic science

counterpart, the National Science Foundation, which was born in 1950, America took the lead in mankind's quest for better understanding of life and mastery of disease. This example soon led other Western European governments to join in escalating their support.

The spawning of new knowledge in such warm and receptive waters was on a greater scale than can be measured accurately. Upon a flood of new facts and concepts there fed new technology. Chemicals came off the shelf or out of jungle plants and became new drugs. New apparatus, growing more powerful and more complicated with each rapid new generation, filled the laboratories.

Old drawings of cells and molecules became wonderlands of detail. The proteins and other stuffs of life fell one by one to molecular dissection. The biologies of man and bacteria were exposed together. Even the genetic code that had presided over the evolution of living things from the beginning was unlocked.

Among the more useful results of all this ferment are:

- that the tuberculosis sanatoria have been emptied;
- and many of the mentally ill returned to their homes;

- that vaccines and antibiotics have nearly banished the dread of fever in a child;
- that the medical care of so many other physical and and mental disorders has continued to improve; and that
- so much of what we have still failed to prevent, from congenital malformations of the heart to shattered bones, are now at least correctible by procedures whose resultant mortality and morbidity steadily decline.

The "mosaic" (of knowledge) will never be completed. In certain areas, however, it is now advancing to a stage of extraordinary refinement. If continuation of the present pace is maintained, we will assuredly have at least a slow, steady return of useful dividends in mastery of most of the stubborn, chronic health problems we recognize today.

From the earliest expansion of Federal funding in the postwar period, emphasis has been placed on support of non-Federal performers. This has led to the development of a national research apparatus extraordinary both for the excellence and variety of the research conducted and for the number and broad distribution of institutions and investigators participating. It has made the great teaching hospitals into

extensive laboratories of human science as well as vastly increasing their power to care for the sick.

The old Strong Memorial is a veteran of these lusty days of bold achievement. As such, it helped to bring about the end of its own time. Hospitals are not renovated; they are enlarged. Yet, people do not grow larger, nor, strictly speaking, do their diseases. It is technology that grows. What was hopeless in older days is possible now. And new opportunities to help must come to be housed in new and bigger structures.

The Old Strong will not envy the changed and expanded responsibilities the New Hospital has inherited. In the years that separate the openings of the Old and New Hospitals there have occurred many other changes.

One of these is an expansion of the definition of health, and therefore of the purview of health care. Once they meant only medical care for the sick...the diagnosis and treatment of specific illness. Now they mean no less than some regulation of the number and fitness of children born into a society, a thorough understanding and improvement of the physical and social environment in which people live and work, the helping of each person to know something of his genetic constitution and how he might best modify his lifestyle to adapt to his

environment and avoid disease, the restoring of function and adaptation when they fail prematurely, the easing of the discomfort of the incurably ill and the aged, and the assuring that when life must end, it does so with dignity.

There have also come about dissatisfactions with access to a health system that has grown more complex and anonymous. And over the fact that there is too much tertiary care, too little primary care or prevention.

Of course, the real national distress with health care is with its soaring cost in dollars--a rate of rise that is faster than the general rate of inflation.

To economists, the cost spiral seems particularly ominous because, if measured by changes in mortality rates or in longevity, there appears to be a steadily declining ratio of benefit to cost. Indeed, there is no question that factors other than medical care, such as housing, pollution, poverty and crime, loom large as determinants of the quality of life or of mortality in youth.

Because of its mounting role as guarantor of health care, the Federal Government has become the single most compelling force for changing the health system toward greater cost-effectiveness. It has strong remedies available

to it, but does not pretend to have the cure. This must be found in collective actions by all public and private interests involved. Basically, the question is not whether, but how far a largely voluntary fee-for-service industry needs to be converted to a pre-paid, highly regulated public service system. The answer is not revealed in any generally adopted strategy. It is being determined largely by a series of political compromises. And at risk of transformation in this process are:

- the traditional ways in which physicians and other health professionals are trained, located and how they are paid;
- the content and style of professional practice and the nature of ethical and legal contracts between physician and patient and society;
- the division of responsibilities between medical schools and their parent universities;
- the financing, the management, the affiliations, even the design of hospitals and clinics; and
- the support and emphases of biomedical research and the growth and uses of medical technology.

All of these areas of change are not concerned solely with cost-effectiveness. A perceptible shift also is taking place in the frame of reference by which human values are

assessed. In a society grown increasingly technological and rapidly changing many of its social norms, reactions are occurring to all kinds of previously privileged institutions and professions. Threats to individual privacy and dignity are now perceived in what man was doing in the name of mankind. And large groups of the population suspect they are underserved.

Thus the medical school and its teaching hospital, and their old custodian, the biomedical sciences, find themselves in 1975 in the path of two movements for reform. One is primarily economic, the other mainly ethical. Perhaps, two more incompatible forces would be hard to find. At least the dilemmas their conjunction creates are unusually perplexing.

For science there are the problems of:

- keeping the maximum freedom for exploration while using public support with the maximum of efficiency;
- striving for optimum application of knowledge to improve the public health;
- explaining fully the processes and products of research that create difficult social choices.

There will be some ceiling imposed on the unlimited ambitions of 50 years ago, and some modification of specific

research goals. It serves no good purpose to ignore the growing perception that the world has a resource problem. Its riches are in fact finite and shrinking on a per capita basis, under irresistible population pressures. The search for new forms of energy and employment force a tampering with the environment that may threaten survival. New understanding of the limits of human adaptation, new guidance for fair and effective regulation, are part of a new mandate for health science.

Another emerging problem, as old as medicine, but growing more pertinent with the expansion of technology, is the development of life - extending palliation of chronic but incurable disease. The problem is again the cost, and delicate questions persist of how much a burden on the whole of society any one of us, as individuals, has the right to be. To expect scientists or physicians to answer these questions for us all is wrong. But they, and those who will staff this New House, must expect a growing responsibility for helping a larger community to develop compromises that protect both individual and societal interests.

In the decades ahead scientists should not be concerned

as a first priority with the extension of man's "normal" life span. There is too little evidence that for most very old people a far longer life means a better one. Nor is it reasonable to expect much gain very soon against the down phase of waxing-waning pattern of life processes. A cure for normal aging is one of the least likely products of biomedical research.

The principal goals of health research, then, come down to this: first, to limit "premature" death--with maximum narrowing of current differences in life expectancy based on sex and race; and second, to minimize throughout people's lives the impact of physical and mental disability, while augmenting positive aspects of health and well-being.

Scientists must also be concerned to provide society with the effective knowledge it will need in order to make meaningful decisions in several critical areas of long-term social policy. These include efforts to provide a better match between population levels and anticipated resources in relation to the quality of environment sought. Also important will be the efforts to move toward a reduction of the burden of deleterious genes borne by posterity.

As for the schools that educate physicians and other

health professionals, they are accused:

- ...of having been seduced by science, of creating an excess of "discoverers" and a deficiency of "carers;"
- ...of training too many specialists and not enough generalists;
- ...of creating further imbalances toward palliation or cure and away from prevention;
- ...of teaching at the bedside and not in the clinic;
- ...and worst, of graduating professionals who understand their work as a craft, but who will not or cannot achieve its integration into a system with greater efficiency and maximal responsiveness.

There is some truth, and much that is hollow rhetoric, in all these accusations. To hold the world of the Old Hospital entirely, or even mainly, responsible for the social and economic problems of the health system is neither correct nor fair. The growth rate of technology and the pace of change in scientific content of medicine and biology has been so great as to be a consuming preoccupation.

The medical schools and their teaching hospitals cannot by themselves guarantee to all an equal access to the best of health. They have neither the resources nor the reach.

What they can do is the following:

- First: they must continue to encompass the ever-expanding centers of highly specialized tertiary care. Continuing research and scientific inquiry of high order is intertwined with this commitment. A heightened responsibility for what is eventually promoted as acceptable for incorporation into health care practice is also implied.
- Second: they must instruct as they have done through the centuries, in not only the scientific arts that bear on disease, but also in the social and humane arts that relieve infirmity.
- Third: they must remain a center for community inspiration and enlightenment in the means for health maintenance. A teaching hospital is a paradoxical institution. It finds it hard to survive unless full. Yet it serves best when striving to keep empty.

The conditions will be tougher and some problems more complex for the New Strong Memorial than they were for the Old. All in all, however, the challenge is but a refinement and extension of the one handed this institution when it was built 50 years ago. To care for people with regard for their need

and not their means...to excel in the region and stay on par with the best in the world...to inspire those who come to it for learning...to imitate the excellence of the past.

Undoubtedly, the New will find the way to respond as magnificently to the difficult premise that one institution must be so many things to a community. In every sense this new house we dedicate now is built on the foundations of the old one.

In George Corner's book "George Hoyt Whipple and His Friends" the story is told that:

"At an intimate dinner of the University of Rochester medical faculty in 1934 when George Whipple won the Nobel Prize, Wallace Fenn, professor of physiology, revealed an unsuspected gift for light verse by reading a parody of The House That Jack Built, telling of the school that George built and all its inhabitants from the dean to his dogs. Brought out again, by request, from time to time, this amusing piece grew by accretion; for the occasion of Whipple's retirement in 1955 Fenn added a new stanza beginning

'With wisdom born in New Hampshire's hills
And a high disdain for useless frills
He sat him down on a three-legged stool,
And man by man there grew a school...'..."

That laboratory stool could have been equally apt as a reference to the essential triad - research, teaching and service.

Today we rededicate Strong Memorial Hospital to these three original and continuing purposes, knowing that we renew an old and effective source of light and comfort and hope. This is the legacy - and the challenge - from the Old to the New.

TRAINING PROGRAMS OF THE
NATIONAL INSTITUTES OF HEALTH: CURRENT STATUS*

Donald S. Fredrickson, M.D.**

It is appropriate for me to discuss NIH training programs with you this morning in view of what I am sure is the general confusion regarding the status of these programs.

In the next half hour or so I am going to try to do two things. First, to give you an overview of the current status of the NIH authority for training as well as of the status of our programs. And second, I want to review with you the general policy issues bearing on the training question, indicate some possible resolutions, and solicit your good advice and counsel on these very difficult problems.

For the past five years Administration questioning of the NIH training programs has become increasingly intense. The problem has centered on three basic questions. First, is there a proper Federal role in the training of biomedical scientists? Second, if there is a role, how does one determine appropriate levels of support and the areas in which personnel will be needed? And third, what are the most appropriate mechanisms through which support should be provided? In response to these general questions, which have been repeated in one form or another on several occasions, the NIH, in 1970, 1971, and 1972

*Presented at Meeting of Association of Professors of Medicine; 86th Annual Meeting of Association of American Medical Colleges, Washington, D.C., November 3, 1975.

**Director, National Institutes of Health, U.S. Dept. of Health, Education, and Welfare, Bethesda, Maryland.

produced a series of voluminous reports on training. None of these seems to have been persuasive.

Parenthetically, if I may digress for just a moment, I want to share with you a paragraph which I came across in a 1968 House of Representatives' report on "Federal Education Policies, Programs and Proposals." The report contains a preface signed by the Honorable Carl D. Perkins, then and still Chairman of the Committee on Education and Labor of the House, who says, "The Federal role in education was long a controversial topic in America. While it can still generate considerable debate, the issue has dwindled to a question of how large the role must be. The basic question of whether there is, in fact, a Federal role has long since been settled in the affirmative." However true that may be for education in general we seem not yet to have reached that state for education in the biosciences.

The issue came to a head in 1973 when the attempt was made to impound training funds and to eliminate all new training starts. The political response to this action was strong enough to prompt the Department to initiate the so called Weinberger Program, which emphasized postdoctoral fellowships. Further, as you know, a successful court suit brought by the AAMC in 1974 forced the release of the training funds which had been impounded in 1973 and these funds together with increases which the Congress had voted for 1974 brought training funds available for that year to a record high. Also as a result of all of this activity the Congress, in 1974, passed the National Research Service Award Act which repealed all the previous training authorities of NIH

and substituted new ones. The extension of this bill has been approved by the House and is now being considered by the Senate. The bill is particularly important at the present time since its provisions will guide NIH training programs for the immediate future.

The outstanding features of the bill are as follows. First, it provides for individual and so called "institutional" fellowships, with at least 25% of the funds to go to the support of individual fellowships. Second, it establishes a three-year limit on the support of any individual. This limit is subject to a possible waiver, however. Third, the bill, for the first time in the context of NIH programs, establishes a service requirement to repay society for the training received. In general, the service is to be provided in the area of health research or teaching, one year of service for each year of training received. In the event that the required service is not provided the recipient will be required to pay back the stipend received during the period of training, with accrued interest. Fourth, training can be provided only in those subject areas for which "there is a need for personnel." The need is to be determined by an extremely broad ranging study which the act mandates to be undertaken by the National Academy of Sciences. Fifth, it specifically excludes clinical training (i.e., "residencies").

The 1974 Bill authorized funds for one year, terminating June 30, 1975, and, as I have indicated, it has not yet been extended. The continuing resolution under which the NIH is now operating contains a stipulation which permits programs for which authorization has not

been passed to continue at "the current rate or the rate provided for in the budget estimates; whichever is lower," in this case \$124 million.

As a result of these events the National Institutes of Health are now administering three separate research training activities. First, there are the old fellowship and training grant programs that were ordered terminated by the President in January 1973 and are still in the process of phase-out. These programs are being honored for the full project period as indicated on award statements and under the terms and conditions in effect up to July 12, 1974. A number of these programs, supporting pre- and postdoctoral trainees, will extend in to 1979. The Court decision on the release of impounded funds during 1974 required the NIH to adjust budgetary requests as approved prior to the phase-out determination and to support applications approved but not funded in 1973.

Second, as I mentioned before, a new postdoctoral fellowship program was announced by Secretary Weinberger on July 9, 1973. This program was implemented under new specifications that required support only in areas of critical need and is now also being phased out.

Third, we have those awards which have been initiated under the National Research Act of 1974, the terms of which I have just outlined for you. Detailed regulations covering the administration of the National Research Service Award Act were signed by the Secretary of the Department of Health, Education, and Welfare in April 1975 although applications had in fact been solicited for the program prior to the final approval of the regulations. Under the continuing resolution, NRSA applications recommended for approval at the June 1975 council meetings are being

funded by some Institutes. In addition, postdoctoral fellowship applications that met the May 1, 1975, deadline are being reviewed now.

I have noted the Act's requirement that awards can be made only in areas of need as specified by a study to be carried out by the National Academy of Sciences. The first report of the Academy, "The 1975 report of the Committee on a study of national needs for biomedical and behavioral research personnel" was received in late June and will be used as the basis for program announcements for this fiscal year. During July and August the Academy report was reviewed in some detail in NIH and awarding Institutes have developed their program announcements. An issuance for the NIH Guide to Grants and Contracts covering training programs has been completed and was distributed on October 24. Many of you may have already seen it; it is quite similar to the announcement which was distributed last year. Based on the language in the continuing resolution, we are requesting applications in time for additional competition during the present fiscal year. If necessary, we plan to have special advisory committee meetings in order to make additional awards for July, 1976. These plans, however, are contingent upon approval by the Department and the Office of Management and Budget and, of course, on the outcome of the FY 1976 appropriation bill. At the DHEW and OMB levels a number of policy decisions have yet to be made regarding the type and number of awards we will be able to make this year.

At the present time, then, legislative authority for the continuation of the training programs of the NIH will reside in the National Research Service Award Act. The House of Representatives has approved

extension of the Act for another two years with only very minor changes. The Senate has not yet acted on it; we have no reason to believe that they will not also approve extension. But two years is not a very long time and the NIH is now in the process of trying to clarify its own thoughts on the problem and to come up with program proposals which will both sustain the conceptual momentum which we believe we have achieved in the support of training over the past fifteen years and be politically acceptable. To accomplish this would be a gratifying achievement. The National Academy of Sciences has issued its first report on training and essentially recommends the continuation of programs at their present level while it undertakes to produce a more thorough assessment of the problem. While we look forward to the recommendations of the Academy and we will certainly be consulting with them on the development of those recommendations, it seems reasonable for the NIH to go ahead on its own at the same time, in parallel. I am not yet prepared to share a fully developed position with you because it does not yet exist; but I can indicate some of the factors which are entering into our thinking.

In exploring the question of the appropriate Federal role in bioscience training over the past five years, a set of propositions has evolved which essentially summarizes the basic arguments in favor of Federal support for training. I am sure that these are all familiar to you, but a systematic summary of them will be useful for the purposes of this discussion.

(1) First, the lynchpin of the argument is that it is generally accepted that support for biomedical research is a proper role for the Federal Government.

(2) Research training can be viewed as a subset of research. It not only produces new crops of trained scientists, but also produces original research as a by product; that is, students carry out legitimate and significant research during the course of their training.

(3) If a continuously forward moving research program is to be maintained, new people must be trained not only to compensate for attrition but to provide for a continuous flow of new ideas. Historically, a significant proportion of the new ideas in science and a very large proportion of the necessary hard work have come from young scientists. The cost of training is justified as an "insurance premium" to assure the continued vitality of the research programs.

(4) Available evidence suggests that the economic rate of return to a biomedical scientist on his investment in graduate training is so low that society must subsidize his training. We have data which show that the rate of return for the M.D. is negative. A study of Ph.D.'s is still underway, but existing information suggests that the problem for them may not be too different.

(5) A healthy, vigorous national program of biomedical research also requires the continued existence of healthy and vigorous training institutions.

(6) The NIH does not believe that it is responsible for the training of all bioscientists, but does believe that it is necessary to support

some reasonable number so that the highest quality students are able to undertake training in the highest quality training environments.

(7) The maintenance of a vigorous biomedical research program is too critical a national issue to be steered by the highly uncertain play of the market.

As the controversy on training has developed the conclusion that there is a proper Federal role in the support of postdoctoral training has gained substantial acceptance. This has not been the case for pre-doctoral training, however, and the objections to it can generally be categorized as "public policy" arguments and "market place" arguments.

In public policy terms the question is posed as: "The Federal Government does not support training in other fields, for example, law and accountancy, why should it do so in bioscience?" In responding to this we could note that in fields in which the Federal Government accepts central responsibility for funding it does, in fact, also accept responsibility for training. The most outstanding example is that of the military. A less extreme example, perhaps, is the traditional role which the state governments have played in subsidizing the training of primary and secondary school teachers. The Federal Government has accepted a central role in the funding of biomedical research, which it has not done in areas such as law and accountancy, and this makes a difference for training. Furthermore, the argument that the Federal Government does not support training in other fields is not entirely correct.

For the past several years the National Science Foundation has conducted an annual survey of the sources of support for full time graduate students in the sciences. The 1974 survey indicates that across all science fields almost 64% of all graduate students report receiving some outside support. In engineering the total is almost 74%, in the biological sciences in general it is approximately 78%, in the physical sciences, 88%, in psychology, 66%, in mathematical sciences, 77% and in social sciences (excluding psychology), 58%. In citing these data I have of course not mentioned one aspect of them in order to make a point. The omission is that the support referred to included not only training grants and fellowships, but research assistantships and teaching assistantships as well.

The point is that a substantial number of all graduate students in science do receive outside support. The "public policy" issue has in fact been decided affirmatively by now. Questions of by what mechanism, how many shall be supported, do remain. I will come back to them presently.

The "market place" argument emphasizes the demonstrable fallibilities in predicting the demand for trained scientists. It, therefore, suggests that the demand itself will eventually lead the right number of people to get themselves trained in the right areas. An argument related to this "theory of the invisible hand" is that it is poor public policy to train people for jobs which may not actually materialize.

We can well agree, of course, that predicting the demand for scientists five to ten years in the future is an extremely chancy business. We might

also add that an exact match between supply and demand is never possible. It is also worth noting that a free market in the funding of biomedical research does not actually exist and that expectations derived from a free market theory may well not be applicable here. The commitments involved in bioscience training are too long. The systems of rewards sufficiently unique, and the needs for steady supply are too great to rely upon a process that is totally laissez-faire in nature. In a profession so dependent upon creativity as is research it is noteworthy that provision of a subsidy for training requires the Federal Government to retain several options. Training support need not be viewed as a job guarantee and it is not proposed that support be provided for all students in the field.

The problem of clinical training as opposed to that for research merits a short digression. Historically, the NIH has focussed its training efforts on research training, although from time to time it has supported clinical training in particular areas. For the past few years the agency has strictly emphasized research training. Federal support for advanced clinical training presents a variety of problems, not the least of which, is the difficulty of responding to the question of why the Federal Government should subsidize the training of persons whose already high incomes may rise appreciably higher because of their training. Such perceptions cannot help but jeopardize training for research where negative income differentials are common, at least among M.D.'s.

The problem of clinical training has not departed NIH entirely. It is a subset of a larger question: The roles, actual and envisioned,

for large comprehensive centers where biomedical research on a particular disease or group of diseases is conducted. Although the nation is seen by many to be returning to the fundamentals and emphasizing the need for primary care physicians, the growth of new technology continues. It is not to the new crop of primary care physicians that more and more of the treatment of many disorders, most notably cancer, is to be entrusted. Rather, the movement is for increasing subspecialization. Where the separation between researcher and such specialists is, perhaps necessarily, blurred, pressures exist upon the research agency to support and provide the necessary training.

Such problems touch upon the matter of centers, and the interface between research and service which much concern me. We have not the time now to engage them deeply, but I would hope we could do so some time in the future.

To return to our emerging stance on training

In general, it is our present belief that deliberately designed programs of training subsidy in the biosciences promise a much more effective, and indeed economical, method of producing the high quality of research manpower which the country requires than could result from pure dependence on the market place. We believe that such a program should include institutional as well as individual awards (that is awards like training grants as well as individual fellowships) and that it should provide for training at both the pre-Ph.D. and post-Ph.D. level, provide research training beyond the M.D. both for clinical research and fundamental research, and provide for a small but well

organized program offering combined degrees leading largely to the M.D./Ph.D. but also for the D.D.S./Ph.D. and the D.V.M./Ph.D.

It is our feeling that such programs should emphasize quality to an even greater extent than they have in the past and that they should be highly competitive. It seems doubtful that we can expect to support programs in all major departments of the country, and perhaps we should not even try to do so. The problem of what is a reasonable number of trainees for which to seek Federal support is of course an extremely troublesome one. To some extent an answer to this question must be arbitrary; but at the same time it is our wish to design recommendations which will have as strong an analytical basis as possible. One way in which one might, perhaps, go about this is by first identifying some reasonable number of fully trained researchers which should be produced annually with Federal support and then using this number as a basis for determining the size of the pipeline needed to produce it. It is not yet entirely clear whether such an approach is feasible but it is being explored. The question of how training resources should be allocated by field is also extremely troublesome. At the pre-Ph.D. level we are coming to believe that the most appropriate approach for the Federal Government is to support broad, interdisciplinary programs which will produce scientists who are not locked into narrow fields. The philosophical base for this belief is twofold: First, that the frontiers of science tend often to be at the interfaces between disciplines as we know them today and second, that since we can not accurately predict what scientific requirements will be five to ten years hence, the soundest strategy is to train scientists in as flexible a way as

possible. The study group of the National Academy of Sciences may well have other useful recommendations in this area.

This then is where we are, with a very brief view of where we have been and a somewhat clouded view of the general direction in which we might be headed. The Administration of the training programs of the NIH has certainly produced its share of frustrations in the past few years but also its share of challenges and excitements.

We are not yet quit of all problems and frustrations. Your institutions will be receiving an official statement on a new problem in a few weeks. Since we are discussing related matters, I will summarize it briefly.

At the present time it is the practice of the NIH and ADAMHA to request letters of recommendation on all fellowship applications as part of the application review process for this program. Under the access provisions of the Privacy Act, these references, including the identity of the writer (the referee), will be available to the applicant on request. It is the view of the NIH and ADAMHA that frank and honest reference reports are critical in assigning priorities and recommending approval or disapproval. We believe that lack of confidentiality will inhibit full and open expression of opinion; that reservations and negative assessments will be buried, or at best, ambiguously blurred, and the resulting judgment will be made with incomplete or misleading information.

For these reasons we requested an exception to the access provisions of the Privacy Act for these letters of reference. The request has been denied on the basis that the grounds for exception provided in the Act do not apply to grant applicants. We will, therefore, in all future requests for recommendations on fellowship applications advise the referee that his comments will be made available to the applicant on request. Quite frankly, we do not know what this will do to the system for reviewing fellowship applications and hence to the quality of the program. At the moment we have no alternative but to conform to the requirements of the Act.

NOTES FOR OPENING REMARKS BY THE DIRECTOR, NIH
BEFORE PRESIDENT'S BIOMEDICAL RESEARCH PANEL, 11/24/75

(Authorities of the Director)

I am grateful to the Panel for allowing NIH to appear before it again and for your having first given me over 4 months to adjust to the climate of Director

Sometimes it is very warm there, but I must say, in candor, that I have been reassured by a close, hard look at this institution and all that it is responsible for. Problems we do have. Some of these I will want to talk to you about later. But on the whole, I am comforted to find myself totally engaged with a competent and self-confident organization. Its mission still seems to be in the best interest of humanity. I am not an expert in management theory but feel comfortable with the proposition that the NIH is reasonably well organized to achieve its research purposes--and to do this effectively and even efficiently.

I am willing to try to answer any questions the panel may have. There are several issues that I specifically wish to discuss with you, and propose that I might introduce one of these now.

The question that I have confronted most frequently in regard to NIH is how biomedical research priorities are established. Part of this question is: What is the Director's role in budget development?

I have several considered suggestions for improvement in this process that I am glad to offer. It requires first that I address the

authorities of the Director, NIH with particular reference to budget formulation and execution.

Basic Authorities of the Director, NIH

The basic authority for most programs of the National Institutes of Health is derived from Section 301 of the Public Health Service Act, dating back to 1944. Numerous additions and amendments to this authority have created the categorical Institutes (mostly in Title IV) established special programs and set up goals or imposed limitations on NIH programs. Most of the relevant statutory authorities under the Public Health Service Act that have been made available to the Director, NIH, have, in turn, been delegated to the Directors of the NIH Bureaus, Institutes and Divisions. Hereafter, I will call them BID's. Similarly, most administrative management authorities which flow to the Director, NIH, from the Secretary, the Civil Service Commission, from GSA or OMB, have in turn been delegated downward. Nevertheless, in the role of Director, I have found that most of the necessary authorities have been retained.

Most of the powers exercised by the Director, NIH may be catalogued under the headings of policy and persuasion, plant and personnel--and each of these, in their way, relate to the activities of priority setting and budgeting.

- . With respect to "policy and persuasion": The Director--at the most practical level--sets policies for all cross-cutting activities of the NIH, both in program and administration.

His is the key responsibility for assuring the integrity of vital NIH systems, including those for review and approval of the vast grant and contract enterprises which are NIH's main business. Whether he wishes to or not, he plays a significant role in setting the tone in certain critical relationships: Those between the NIH and centers of executive and other political power; and between the NIH and the broader biomedical research community. He is challenged, in these relationships, to interpret and persuade in both directions--inwardly, to the sources of research strength in the community, and outwardly to deciders of public policy, so that needs and expectations from both perspective may be better understood.

- With respect to "plant": The Director, has a number of authorities that derive from his role as manager of the NIH reservation at Bethesda. In this role, he makes the final decision on allocation of office and research space to the various NIH components. He also decides on the use of other shared resources, including the Clinical Center.
- As for personnel: The NIH Director appoints the Directors of component Bureaus, Institutes and Divisions (except for the Director of the National Cancer Institute, who is appointed by the President); and must approve appointments and promotions of senior professional staff in the various NIH components.

The Director also manages the allocation of personnel employment ceilings, but cannot exceed authorizations of budgeted positions in prospective appropriations.

Now let us turn to budget authorities:

There is no reference to the Director, NIH, in any of the basic statutes, appropriation acts, or other legislation which expressly gives him authority to determine size of budgets or permits him to re-program or to spend funds appropriated to NIH Bureaus, Institutes, and Divisions. Nevertheless, as will be seen, the Director has a significant role in budget formulation and execution.

The NIH budget consists of 14 program budgets and several housekeeping items. About 6% of total funds, excluding Buildings and Facilities, are reimbursed by the BID's to the NIH Management Fund and General Expense Accounts for logistical and support services.

Each year, the Director and his staff assemble budget proposals from the separate program elements. The Director constitutes the last level of review and decision-making in the course of formulation of the NIH budget as submitted to the Department and the OMB. The NCI budget presently bypasses this process.

At this time the manner of distribution of the "uncommitted" funds is the major way in which the Director, NIH, modifies and influences the

"President's Budget" which in turn is the base upon which any congressional increases occur. Decisions are made with regard to the proportion of these funds going to national and congressional priorities. Of prime importance, however, is the ability to emphasize the need to protect and encourage areas which are not likely to receive adequate attention otherwise. [These include such areas as environmental health, allergy and infectious diseases, general medical sciences.] High priority is also assigned to assuring an appropriate funding level for "new starts" (to protect the input of new scientific blood and ideas); and to the need to upgrade and maintain the intramural program.

It is my impression that the Director, NIH, is in a unique position to influence policy on the budget and priority-setting process. He is at the intersection of most of the diverse ambitions and interests of all of the constituencies seeking support for biomedical research. His is the first level of review which is programmatically neutral or impartial and the last at which scientific considerations are the main determinants of program decisions. If he is ^{an}~~a capable and~~ experienced scientist, listens attentively, and is careful to retain his objectivity and impartiality, his opinions and those of the persons who advise him will represent quite probably the best, technical assessment of the probabilities in relation to research priorities. Beyond him the decisions become remoter; inevitably they also become more political and sentimental.

The influence of the Director in budget processes is, of course, constrained wherever Executive Branch policies or congressional directives specifically limit program flexibilities. Instances of this would include OMB decisions to phase out of General Research Support awards, and combined statutory and Administration limitations in the research training area.

The responsibilities of the Director, NIH, for effective "technical overview" and "adjustment" of the budget will be of more rather than less importance as we move toward the 1980's, through periods of predictably slow program growth. Yet there is real risk that this ability to set priorities will cease to be effective or perhaps even operational unless certain changes are made.

I believe there are a number of possible options for improvement of priority setting processes in biomedical research. You have considered several. I will continue here with the matter as it concerns the Director, NIH, and go directly to my considered recommendation. It consists of two parts:

1. The first is to establish a meaningful advisory apparatus to interact with and support the Director, NIH, in the exercise of his responsibilities for the national biomedical research efforts. To be "meaningful," I believe that such an advisory group should have these characteristics:
 - o Assignment of a statutory role in overview of the NIH program, with specific features borrowed from models provided by the National Advisory Cancer Board, the

President's Cancer Panel, the NLM Board of Regents, and the National Science Board. Specific reporting and program and budgetary review responsibilities probably should be a part of this package; but others should be considered.

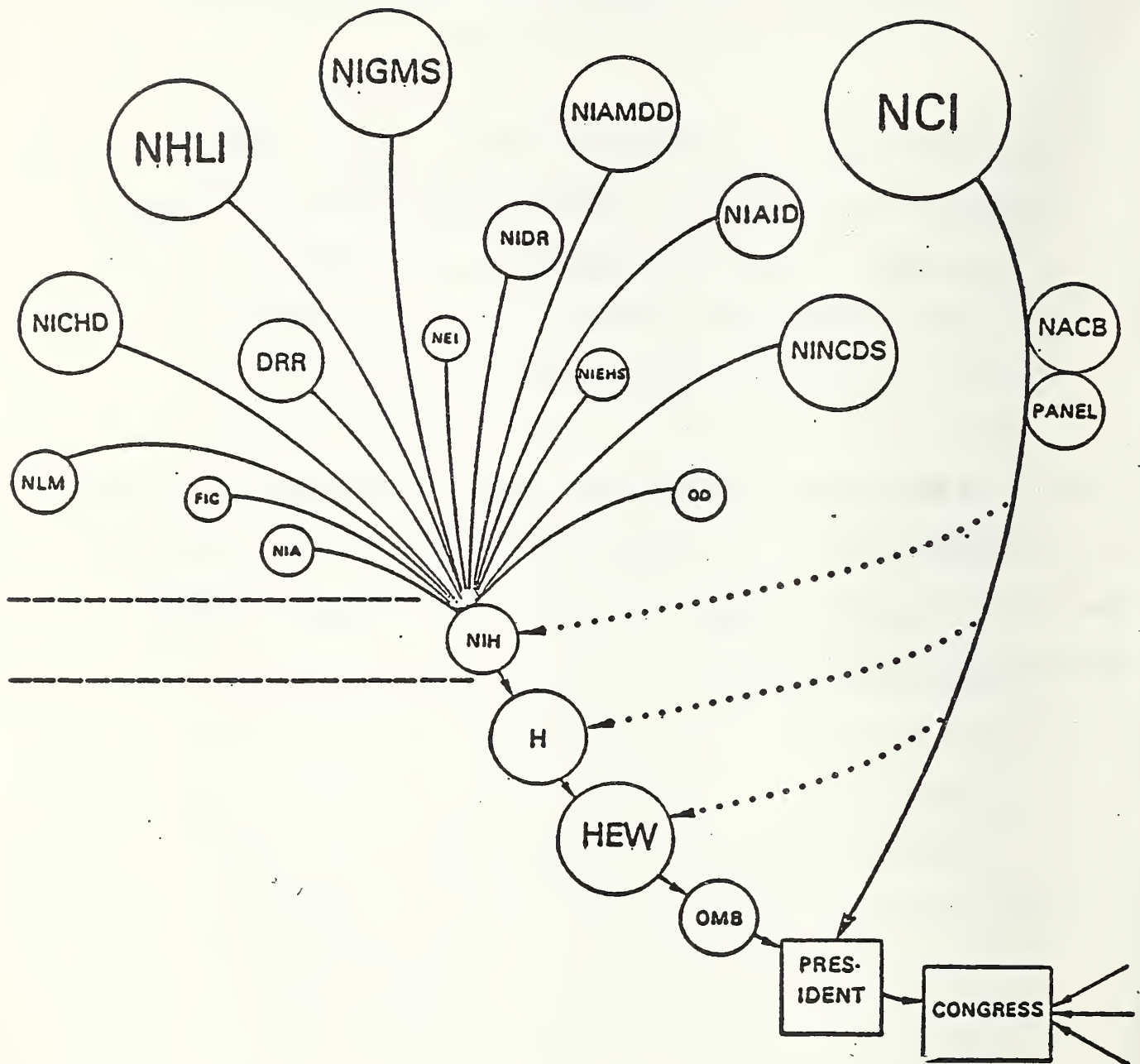
- o Presidential appointment of members, with appointment to take into account eminence, outstanding competence in relevant areas, and willingness to serve. The principal representation should be from fields directly relevant to the NIH research mission--with perhaps two-thirds from the biomedical sciences--but with strong representation also from other relevant areas such as law, economics, ethics, and public policy determination.
- o Appointment of 4 or 5 ex-officio members would also be appropriate. These might include one representative each from several of the existing NIH National Advisory Councils, plus the Director, NSF and someone from the President's Science advisory apparatus, if this is re-established. For Chairman of the Group--to be appointed by the President--one would be happy to see someone of the caliber of Mr. Benno Schmidt.
- o The Advisory Group should also be expected to arrange for the conduct of state-of-the-art (or needs-and-opportunities) surveys across NIH program areas, when these are needed to .

assist in priority setting; and to further arrange for cyclic review of the quality of science being supported across the full range of NIH programs.

2. Second, is to provide the Director, NIH, with specific limited authority to re-program funds between appropriations when adjustment of priorities—or need to meet unusual opportunities—would justify this. The new advisory body would be expected to work with the Director in the exercise of this discretionary power.

I will stop at this point to permit questions or extensions of my remarks on this problem. Later, at your discretion I would like to discuss the boundaries of the NIH mission, some points about its direct research and any other topics you wish.

BUDGET PATH -



12/9/75

CONTROL AND DEMONSTRATION PROGRAMS
Second in a Series of Papers on
Areas of NIH Responsibility and Opportunity
By Donald S. Fredrickson, M.D.

- I. To define the role of NIH in control and demonstration activities, we might first consider the boundaries of NIH missions.
 - A. By tradition and law, the primary mission of NIH is to conduct and support research on the major health problems of man.
 - B. Secondary missions are also set forth in statute, and these have varied in NIH history.
 1. Examples are programs to control disease in the population through direct intervention or demonstration of new technologies.
 2. In defining NIH responsibility in the secondary missions, the degree to which their pursuit may be expected to further the primary missions is a significant factor.
- II. Graphically the boundary of NIH activities may be viewed as a bi-layer.
 - A. The inner limit defines functions integral to the development of new knowledge, including all stages of research on disease--basic, applied, developmental--and such auxilliary activities as research training, research communication, and provision of research resources.

B. Between the inner and outer layers lies a zone of mandated activities that have borne over time a protean relationship to the central NIH mission.

1. Some of these activities have been conducted by NIH as a matter of organizational expediency--for example, support of the education of health manpower.
2. Some contain a function essential to research, such as the administration of the National Library of Medicine.
3. Others are extensions of the research mission, in that their object is to help bridge the gap between discovery and application.
 - a. In this area--the "interface" between health science and health care--NIH has an explicit or implicit responsibility that may best be met through control and demonstration programs.
 - b. In the case of the Cancer and Heart Institutes, this responsibility is stated in the 1971 and '72 Acts:
 - (1) "The Director of the National Cancer Institute shall establish programs as necessary for cooperation with State and other health agencies in the prevention, control, and eradication of cancer."
(P.L. 92-218, Sect. 409). Other language of the National Cancer Act of 1971 authorizes "demonstration of advanced diagnostic and treatment methods" (Sect. 408).

(2) The National Heart, Blood Vessel, Lung and Blood Act of 1972 expresses the authority in greater detail [P.L. 80-655, Sect. 413 (a)(4), (5), (7), (8), (9), (10); Sect. 414; and Sect. 415(2)].

- c. The recently passed Diabetes and Arthritis Acts (1974) contain congressional mandates for control and demonstration programs in diabetes (P.L. 93-354, Sect. 3) and arthritis (P.L. 93-640, Sect. 4), but assignment of responsibility for their conduct is discretionary with the Secretary.
- d. The other NIH Institutes would probably have sufficient authority to conduct control and demonstration activities if they wished to undertake them. The fact that no Institutes did from 1961 to 1971 was a PHS/NIH policy decision.
 - (1) With respect to the Dental Institute, specific authority to "cooperate with State health agencies in the prevention and control of dental diseases and conditions" has been in the Public Health Act since 1948 (P.L. 80-755, Sect. 422).
- e. All the other Institutes and Research Divisions have at least an implicit responsibility to see that the fruits of their research are effectively made known to the community of medical practice.

III. The extent to which NIH should engage in control and demonstration activities when these are not specified in legislation must be decided

in the light of the broader missions of the Public Health Service.

A. Due consideration of

1. The programs, expertise and resources of NIH,
2. Those of other Federal agencies with similar and complementary functions, and
3. Most importantly, the persistent defects in the national health system (or non-system)

B. Lead to the conclusion that NIH should conduct control and demonstration programs when compatible with the missions of the cognizant Institutes and under certain limitations.

1. To protect the primary mission of NIH, it is essential that these activities
 - a. Be funded separately,
 - b. Not include regulatory functions,
 - c. Not commit NIH to provide routine medical care, and
 - d. Be reviewed no less critically than research operations.

C. The reasons why NIH should continue these activities are twofold:

1. An inescapable need for transfer of scientific information and technique from the experimental to a practical mode, and
2. The fact that NIH may be the most effective agency for this in the current health system.
 - (a) The involvement of NIH is partly due to the absence of other ways to update and reeducate health professionals quickly,

(b) Accounting for a high moment of inertia in health delivery mechanisms.

D. There are dangers to NIH engaging in such "extension activities."

1. Imperfect protection of the resources needed for research (a funding danger),
2. Risk of bias inherent in a single agency both producing and distributing interventions.
 - a. An important validation step may be missing. New developments should be "sold" on their merits to an independent and discriminating purchaser.
 - b. Required disinterested review of control and demonstration activities can substitute only partly for the more desirable open system.

IV. A better definition of what is meant here by "control and demonstration" is in order.

A. First we might look at the total "health spectrum"--the steps in transfer of new knowledge and technology from basic research to application in health care.

1. The process begins with basic research, preclinical or clinical, which yield knowledge generally relevant to health and disease.
2. Next in the spectrum is applied research, again pre-clinical or clinical, in which the knowledge is applied to specific health problems. (The terms "basic" and "applied" are relative in this context, and precise

definition is not necessary here.)

3. "Developmental research" implies the elaboration of known principles through an engineering process in order to produce a usable product or technique.
4. Clinical trials are a special case of applied research.
 - a. As the term implies, they involve the use of human subjects or tissues.
 - b. The study is controlled by a specific approved research plan, or protocol.
 - c. Successive trials may be undertaken using progressively larger groups of patients in various settings, with a view to establishing efficacy and feasibility of the innovation.
5. Up to this point in the health spectrum, funds authorized for research are applicable.
6. Field testing--the final testing phase--is intended to establish efficacy and feasibility of large-scale application in a community (or non-research) setting where expertise and resources are likely to fall short of teaching/research standards.
 - a. Feasibilities to be studied include cost aspects of large-scale implementation and problems of transferring required expertise to local health professionals.
 - b. Although the field trial is addressed to acquiring knowledge, it falls in the interface between research and health care with respect to the kind of information

sought and its purpose. Thus it may be regarded as a research operation appropriately supported with non-research funds.

7. Demonstration, a means of introducing new technology, clearly falls in the interface. With research and testing phases completed, a demonstration program in a selected community setting may be undertaken.
 - a. Its principal impact is in the education of local health professionals, and its intent is to establish the new regimen in local health practice.
 - b. As in the case of field trials, non-research funding is indicated.
8. Health services research may be defined broadly as the systematic investigation of alternative modes of health care, particularly with respect to the organization, financing, evaluation and utilization of health services.
 - a. The research is designed to choose among methods of intervention, to plan mechanisms of delivery, and to evaluate results.
 - b. The scope includes personal, sociologic, economic, and administrative data that are usually outside the purview of conventional biomedical research and development.
9. Health care is the end product, the final phase of the health spectrum. It implies delivery of the innovation to the patient by health practitioners.

B. Control programs are not necessarily a part of the health spectrum for all innovations. But they play a vital role where spontaneous transfer to the private physician or hospital would be slow or inappropriate.

1. "Control," in the broadest sense of the word, connotes the prevention or conquest of a disease or other health problem in the community.
 - a. The concept has a status gained early with respect to acute infectious diseases, where much of the success was derived from quarantine, regulations, required reporting, and other legal power over human behavior.
 - b. Such weapons are not applicable against most chronic diseases today.
 - c. Basically the term "control program" now means the extension or diffusion throughout the health care system of an intervention, technology, or other change in the substance of health care practice.
2. Demonstration is a technique of health control programs. It may be the only effective action for programmatic control of a chronic disease. "Demonstration" can be taken to mean activities designed to illustrate
 - a. That something which works in an ideal setting also works in a practical one, or
 - b. That something works.
 - c. The former purpose may be served by a field trial;

the latter, by health education.

- d. In the current NIH lexicon, "control" connotes "demonstration" for the most part. It is less ambitious than, say, the classic PHS programs to control venereal disease and tuberculosis, which support measures in State health departments aimed at direct control of disease in the population.
 - e. The main objective in NIH control programs today is to induce medical practitioners and hospitals to take up new methods of diagnosis and treatment, bridging the gap between research and practice.
3. Current trends in medical care are interesting here.
- a. There is a tendency to rely on special centers to care for specific diseases.
 - b. These tend to be the centers established primarily for research.
 - c. And the increasing demand for universal access to the "best of care" creates pressures for more such centers, in broad demographic distribution.
 - d. Their dispersion is limited, however, to the extent that ideas, research funds, and trained and competent people are limited.
 - e. Dissemination of the new technology may still occur through the demonstrations that such centers can provide.

- f. Locally, they transfer innovations to the professionals within their sphere of influence.
- g. If the community includes a medical school, the amplifications serve a threefold purpose:
dissemination, research and teaching.

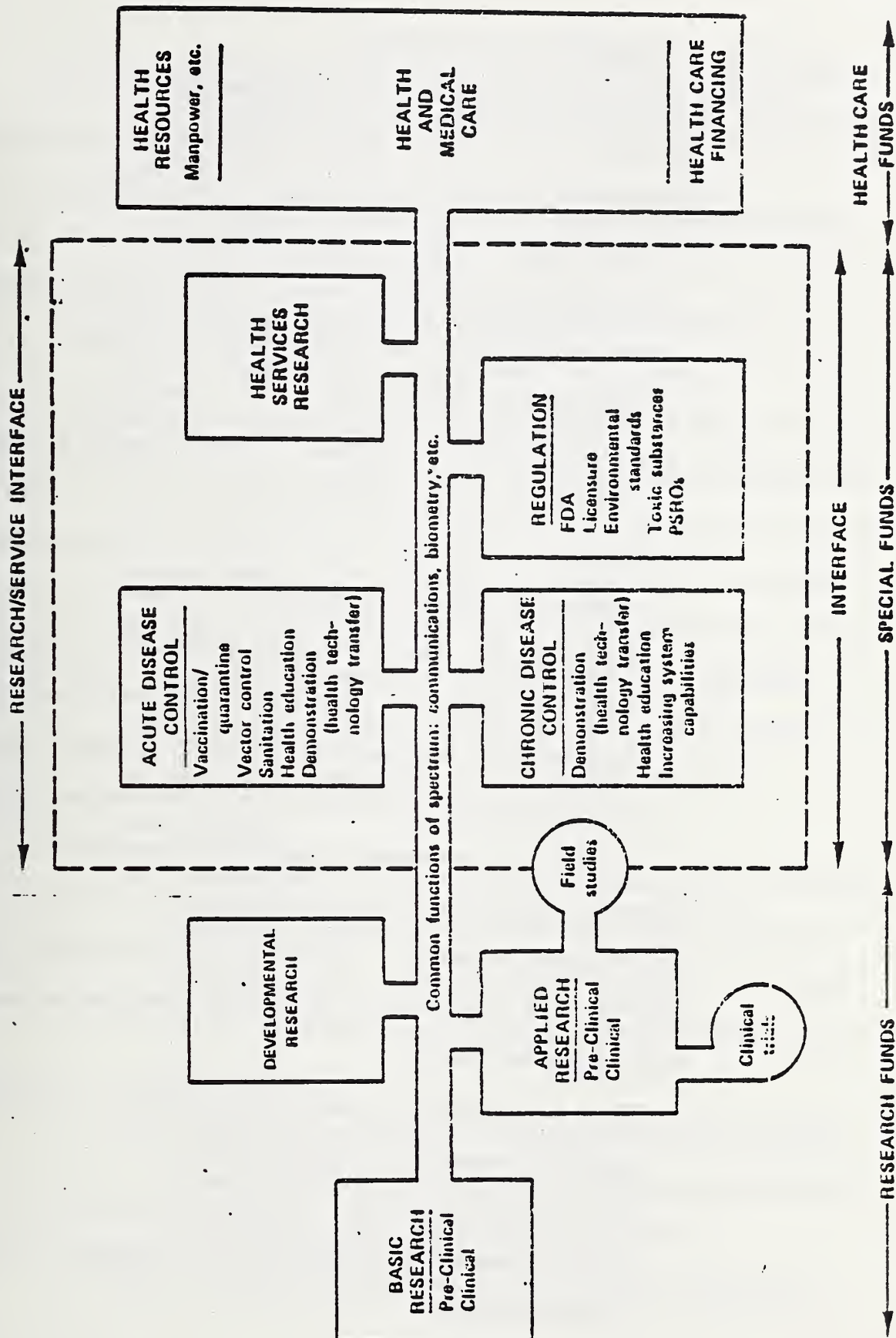
C. "The Health Spectrum" (diagram) shows all the elements heretofore mentioned.

1. In addition, the common functions of the spectrum--communications, biometry, etc.--are represented along the main axis.
2. Regulation, an essential step in the research/service interface, is introduced.
3. The appropriate sources for funding are indicated along the bottom.

D. Characteristics of control programs

1. Are also indicated in the diagram, under "acute" and "chronic disease control." Some infectious diseases, chronic in nature--say, tuberculosis--share characteristics of both categories. Some control techniques encompass both acute and chronic diseases, such as health education, particularly where the message is aimed at prevention.
2. Control activities that are more global than simple demonstration differ materially from experimentation.
 - a. They need more zeal than scepticism and
 - b. Often require expertise and associations that biomedical

THE HEALTH SPECTRUM



scientists do not possess.

3. In the transactions involved in disease control, it is advantageous to have the agency of dissemination independent of the agency of development, and of equal competence.
 - a. The changing substance of medical care should not be determined in a closed system, artificially protected from validation in the marketplace of practice.
 - b. Mistakes can easily be made. The decision of an NIH Institute to promote a certain diagnostic test is a case in point. Intuitively the objective seems eminently desirable. Yet careful examination fails to reveal a definitive validation of efficacy and cost-effectiveness. There are even questions of risk in relation to benefits. Finally, the data basis appears inadequate for determining the effectiveness of the test in the population to which it would be extended. The need for an independent judgment is manifest.
4. Control programs are not necessarily the province of experimental scientists. Where agencies other than NIH exist for this purpose, they should be strengthened and encouraged to serve it.
 - a. When the function is best served by NIH, it should be supported separately from research.
 - b. And the requirement for objectivity and scientific method must not be mitigated in our conduct of this "other mission."

5. A number of essential conditions must be fulfilled before successful control programs can be mounted. Chief among these are
 - a. The availability of an effective method of prevention, diagnosis or treatment;
 - b. Adequate resources of funds and manpower;
 - c. An organization commitment to the goal.
6. In the complex decision process leading to the development of a control program, the first consideration ^{is} whether the particular technology is "ready" for transfer to the health care system. The decision is based largely on scientific grounds, with due consideration of cost and other factors.
7. The next step involves an examination of the intrinsic nature of the validated technology, in order to determine its degree of complexity and the proper mode for translation.
 - a. Conventional methods of dissemination may be deemed adequate if the technology and the factors involved in its adoption are relatively simple--e.g., a new drug that is relatively free of harmful effects and is easily administered.
 - b. There may be need for a structured control program if the technology is complex and requires professional education and extensive logistic support.
8. NIH is eminently qualified to provide the assessments

leading to the above decisions and should play an active role in this important process. Directors of Bureaus, Institutes and Divisions, aided by advisory groups, are usually in the best position to make the necessary judgments.

9. Once the decision is made that a control program is feasible and necessary, two options are open:
 - a. NIH may solicit the active participation of an appropriate agency with direct responsibilities for disease control, or
 - b. May elect to mount the necessary program to accomplish the transfer if no other agency is able to do so and the potential and urgency of the opportunity are sufficient.
10. When the essential scientific conditions for intervention exist, attention must then be directed toward ensuring the availability of manpower, facilities and funds to meet the demands of a disease control initiative.
 - a. Many control activities, involving a significant number of individuals at risk, require large numbers of well-trained health professionals, technicians, and other public health personnel, and extensive logistics support.
 - b. Adequate financing must be provided from the outset.

- (1) It is important that the funding for control activities be separate, to avoid creating serious competition for research funds.
- (2) Conceivably, the control funds could be provided on a revolving or ad hoc basis to accommodate budget fluctuations resulting from the uneven, and largely unpredictable, emergence of scientific opportunities.
- (3) Planning should include provisions for the financing of services after the demonstration phase as been terminated.

VI. PHS disease control programs.

A. In FY 1975, PHS budgeted about \$30 million for disease control programs (excluding those of NIH). This provided the following activities:

1. In ADAMHA. . . . [1 or 2 sentences each].
2. CDC.
3. HSA.
4. RMP.
5. Office of Child Development (OCD), OS, DHEW.
6. Office for Maternal and Child Health, HSA.

B. At NIH disease control programs are currently supported by two Institutes--the National Cancer Institute (NCI) and the National Heart and Lung Institute (NHLI). In fiscal 1975 NCI provided \$51.5 million, and NHLI \$19.6 million.

1. Currently the NCI programs give priority to efforts seeking
 - to increase public understanding of the hazards of smoking and to motivate people to avoid them
 - to identify additional high-risk groups
 - to increase demonstrations by State health departments of the use of cytology to promote early detection of cervical cancer
 - to demonstrate the effectiveness of mammography and palpation for early detection of breast cancer
 - to demonstrate and promote techniques for treating acute leukemia, Hodgkin's disease, and non-Hodgkin's lymphomas
 - to demonstrate techniques for managing breast cancer and cancers of the head and neck.
2. NHLI's control projects, conducted in collaboration with several other agencies public and private, are designed
 - to motivate adults to have their blood pressure checked and, if found to be hypertensive, to seek proper therapy
 - to identify individuals at risk of arteriosclerosis and to motivate them to take lipid-lowering drugs and modify their living patterns
 - to modify the smoking habits of individuals at risk
 - to educate the public about sickle cell disease and Cooley's anemia and to demonstrate techniques for appropriate screening and counseling.

3. Scope of activities.

- a. The NIH disease control projects are limited both in the scope of activity and in the period of support that NIH is to provide.
- b. The manner in which the National Cancer Act of 1971 was interpreted to define the boundaries of the NCI mandate to undertake control activities served to shape a large part of the present concept of NIH control programs. The Office of General Counsel (OGC), DHEW, interpreted Section 409 of the Act to mean that the "Cancer Control Program has essentially a three-fold purpose: (1) evaluation of the effectiveness of research and development of findings through demonstration projects involving controlled community groups, (2) communication of successful research and development and demonstration findings to practitioners of medicine and public health, and (3) education of practitioners and laymen about cancer."
- c. The Office of General Counsel's interpretation further stated that the "Cancer Control Program would not be used to support activities involving: (1) delivery of medical care where the effectiveness of such care has already been well established, or (2) even where the effectiveness of the medical care involved has not yet been well established, delivery of such care to

populations larger than that reasonably necessary fully to demonstrate the effectiveness of such care."

- d. Clearly, the concept of disease control programs as essentially restricted to demonstrations of innovative technology through controlled, time-limited projects conducted in limited populations provides an important distinction between such programs and the provision of service qua service.
 - e. To assure that the conceptual distinction between control programs and service activities does not become blurred when translated into operating programs, the NIH has adopted a stringent policy of limited funding. Individual projects are limited to awards for periods ranging from 3 to 5 years. For most projects, this time period should be sufficient to permit conclusive results. For those projects that, by virtue of their intrinsic nature, require longer periods, the NIH funding is clearly viewed as "seed money" and local support is required for continuation.
4. Evaluation.
- a. Evaluation is an ongoing component of the current NIH control programs.
 - b. Individual projects involved in field testing and evaluating the effectiveness of potential control technology contain evaluation plans as an integral component. In fact,

these projects are essentially evaluative research studies.

- c. Evaluation of the large community-based cancer control programs will be accomplished with the aid of a comprehensive population-based data system. This includes known epidemiologic characteristics of the cancer problem in the community, and will enable NCI to monitor the progress of a program and assess the impact of intervention activities.
 - d. No definitive plans exist at this early stage for an overall assessment of the control program.
5. Dissemination of health information. Based on recommendations of a Committee on Dissemination of Research Results, NIH will take three specific actions for improving the communication of new knowledge to the health professional:
- a. Feasibility studies of the concept of regional centers to promote telephonic consultative service for health professionals.
 - b. Full utilization of new communication technology.
 - c. Expansion of NLM's National Biomedical Communications Network.

VII. Recommended position. It is recommended:

- A. That NIH should play an active and direct role in assessing the adequacy of potential disease control technology,

B. That it should determine, in consultation with experts, the appropriate condition for introducing new technology, and

C. That when the new technology is judged to be effective, feasible, and appropriate for introduction into the existing health care system, NIH should

(1) Solicit the active participation of an appropriate disease control agency or

(2) Seek separate additional funds to mount the necessary control program.

Doing Better and Feeling Worse

Health in the United States

Edited by JOHN H. KNOWLES, M.D.



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DONALD S. FREDRICKSON, M.D.

Health and the Search for New Knowledge

THE EXTRAORDINARY GROWTH in biomedical research and development of the past quarter-century seems now to have ended, and it is likely to be followed by a period of reassessment and adjustment. The choices made regarding the support and direction of the now vigorous research apparatus over the next decade will be critical for the future health and productivity of the medical sciences. And biomedical research today determines medical practice tomorrow. From results of research come the means of improving the quality of health care and, ultimately, of reducing its costs.

Yet the ready translation of the findings of health research into benefits for patients is limited. A great deal of research cannot be coupled directly to the solution of health needs, and only a small fraction of the yield at any one time is convertible to useful technology. Moreover, the application of new medical technology is far more tedious and complex than is generally realized. In contrast to the relative ease with which many infectious diseases are controlled by immunization and antibiotics, the use of drugs and devices to combat chronic diseases can be costly in both time and resources. In addition, the price of technology is often too high in the short term, or too high in terms of its benefits.

The last quarter of the twentieth century will find scientists, health-care providers, and consumers drawn into a much closer community of interests. These will include: (1) field trials to examine, in statistically valid terms, the potency and safety of new medicines, instruments, and techniques; (2) far more extensive health education, emphasizing individual responsibility and the relation between benefit and cost; and (3) an increasing awareness of environmental hazards, and an increasing ability to assess genetic differences among individuals in their adaptation to the environment.

Because innovations in the system can only be evaluated through sensitive measurement of changes in the health of populations, data about people and the results of their encounters with the health system will have to be gathered on a vastly larger scale. The health of Americans is much affected by social and economic factors and by the choices people make in the way they live. These are now beyond the realm of conventional biomedical research; should they be included, debate about the ethical and moral aspects of such research is likely. By the nineteen-eighties, competition for resources can be expected to decrease that part allocated to science, threatening the pursuit of new research at a time when revolutionary techniques such as cell hybridization and fast-reaction measurements (among others) are reducing the gene, the cell, and even the brain to molecular terms.

In the next decade the research community must demonstrate its ability to

improve the health of the population, while displaying a due regard for the costs of health-care procedures and the competition for finite resources from other social imperatives. This carries with it a degree of responsibility for the substance of medical practice never previously sought or accepted by the research community. It is vital that these new demands not be allowed to interfere with the free-ranging inquiry which is still the most critical element in biomedical research.

The United States can take particular pride in its support of the biological sciences and their adaptation to medicine, because there was no established tradition for it in this country's origins. The Declaration of Independence is silent on the subject of science, and the Constitution mentions it only with reference to patents. During the first century of the republic, we were therefore simply the passive heirs of the biomedical tradition of Western civilization. The outstanding advances of the nineteenth and early twentieth centuries, such as those dealing with respiration, metabolism, homeostasis, the Roentgen ray, bacterial causation of disease, and the life-saving possibilities of vaccination and asepsis, were products mainly of Western Europe. The contributions of American medical science accelerated, however, during the first decades of this century. Important advances were made in microbiology, immunology, tissue culture, nutrition, and chemotherapy. But the United States did not take the lead in the field until after World War II, when it did so with explosive force. Its contributions were especially notable for their richness of detail in exposing the complexities of biomedical subjects, and they were made possible by an intensive, large-scale effort unstintingly supported by a high level of technology.

This dramatic growth is attributable to the acceptance by the public of responsibility for research financing. As late as 1945, the only significant support was provided by the Rockefeller Foundation and a handful of other private philanthropies, pharmaceutical firms, and the modest endowments of a few hospitals and universities. Government funding was limited essentially to military medicine and a small National Institute of Health (NIH). The latter, established through the National Cancer Act of 1937, was expanded when university contracts were transferred to it at the termination of the wartime Office of Scientific Research and Development. While originally this move was meant to be a step toward the phasing out of wartime activities, its research soon revealed how scientific knowledge could be stimulated by national support and this led to its continuation and expansion. This far-reaching decision forged strong ties between academic science and the federal health missions.¹

Congressional authorization to pluralize "Institute" in the NIH title came in 1948, when programs to explore heart and dental diseases were added to the existing program of cancer research. The growth of the National Institutes of Health after that date has been much documented elsewhere.² Between 1950 and 1975, United States expenditures for health research and development increased from about \$160 million to more than \$4.7 billion, with the government providing almost two-thirds of that amount. The country, once committed, has also been generous in its support of biomedical-research training and the institutions that conduct it. The National Science Foundation was created in 1950. Its provision for broad federal support to both the natural and social sciences included a relatively modest but important contribution to the vitality of the basic biological disciplines. Although the data are inadequate for valid comparisons among nations, we may safely say that no other country has shown greater public concern for these endeavors.

The expanded federal support of biomedical research had three principal aspects. The first was the development at Bethesda, Maryland, of a scientific center, which was to become the largest biomedical research facility in the world, with a diversified program in the major disease categories. NIH laboratories and clinics soon contributed a steady flow of talented investigators to the nation's medical schools and other research institutions. The research undertaken directly by NIH and other federal agencies probably represents about a tenth of the full-time scientists, floor space, clinical beds, and money devoted to biomedical research in America.

The second aspect was represented by the emphasis placed, from the earliest expansion of federal funding in the post-war period, on the support of scientists outside government. This led to the development of a national research effort that was extraordinary for both the excellence and the variety of the research conducted and for the number and broad distribution of institutions and scientists participating in it. In this development, a special role fell to the medical schools, which from the outset had received about half of the awarded funds.³ Here a dual purpose was served: the research which the government paid for not only advanced knowledge, but significantly enhanced teaching programs to the eventual benefit of medical practice.

The third aspect—and the one ultimately supporting the quality of all these efforts—was the adoption of a policy supporting projects that were initiated by an investigator but evaluated through a system that ensured objective selection by a committee of peers. This system was, and basically still is, at the heart of federal biomedical-research policy, although minor modifications have been made to reflect current trends in research support and organization.

In 1975 about \$4.7 billion was spent nationally on health-related research and development. Of this, 60 per cent came from the federal government and 12 per cent from state governments, voluntary health agencies, foundations, and other sources. The rest was derived from industry. It was nearly all used by its donors for explorations ranging from basic research to the development of new commercial products, and was concentrated in the pharmaceutical industry. While industrial concerns are not presently eligible for Department of Health, Education, and Welfare grants, they did receive \$270 million in federal contracts for health research in 1975.

A lack of precise knowledge about these industrial activities forces us to concentrate here on nonindustrial developments. There, it is clear, the American public is the major supporter and the university the major performer. In 1975 about \$1.4 billion flowed from federal agencies to academic institutions (and to the hospitals they own) in support of health research. The NIH supplied about three-quarters of this sum. The rest came mainly from other HEW agencies, the Energy Research and Development Administration (formerly the AEC), NSF, NASA, and the Department of Agriculture.

The principal federal agency responsible for behavioral science is HEW's Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), which has been independent of the NIH since 1967. Its research expenditures for fiscal 1975 were \$139 million. In that year the NIH spent an additional \$25 million for behavioral and social research. We may expect to see both agencies increase their support for, and conduct of, such research, for there is evidence that psychosomatic illness, the role of human motivation in health needs, family planning, aging, and other sociobiological phenomena will become progressively more amenable to biological description. The President's Biomedical Research Panel is considering whether ADAMHA's research

program, some of whose activities are now conducted in NIH facilities, might not benefit from being returned to the full responsibility of the NIH.

Between 1965 and 1975 the federal government met almost two-thirds of the nation's health-research costs, and the NIH budget steadily accounted for between 55 and 65 per cent of the federal share. The proportion contributed by private, nonprofit donors declined slightly, while industry's share rose from about 23 to 28 per cent.

Several economic trends in recent years are important to biomedical-research support. For example, the enterprise has not escaped the impact of recession and inflation. Unlike the research in industries based on advancing technologies, biomedical research cannot be justified through profits from the sale of products. And the "market" of total health cost, to which research is often linked, has the anomalous property of inspiring general regret at its unremitting growth. It would seem that research should be increased as the market expands and should ultimately reverse the trend as total health costs are reduced by new technologies, particularly as a consequence of disease prevention. However, a relative decline in research expenditure has even now actually occurred. Total health costs in America rose more than threefold between 1965 and 1975 (\$39 billion to about \$120 billion), while the percentage of the total represented by health research declined from 4.8 to less than 3.9 per cent. This shrinking of the proportion of the health dollar spent on research is likely to continue. Not only can the rise in health costs be expected to accelerate, particularly if national health insurance is introduced, but the federal share of these costs will probably grow, greatly increasing competition for uncommitted public funds.

The reduction of life in all its complicated forms to certain fundamentals that can then be resynthesized for a better understanding of man and his ills is the basic concern of biomedical research. Although increasingly complex technology is utilized, biomedical research, like all scientific work, is dependent upon human creativity. That ideas, curiosity, hard discipline, and effort are essential is reflected in the application of about 70 per cent of the total direct cost of research to the payment of the individuals involved.

Research is the making of observations under conditions designed to establish relationships with exacting requirements for proof. Substantial knowledge and experience, some of it learned only by apprenticeship, are required. The sophistication of modern research demands that more and more of it be done by full-time professionals. If they are also trained as practicing physicians, they must choose between scholarly recognition and the larger income gained in private practice.

The American supply of biomedical-research manpower comprises about 90,000 doctoral scientists—six times as many as in 1950.⁴ About 60 per cent are academic scientists (i.e., Ph.D.s) and most of the rest are medical doctors (1971 ratios). About half of these latter are on medical-school faculties, and about 70 per cent of the former are on the faculties of either medical schools or other educational institutions. A little more than a tenth of the total supply is employed by government.

While the location, number, and kinds of scientists can be reasonably estimated, there is no fully satisfactory description of the more general task in which they are engaged. It resembles the construction of a vast mosaic comprising myriads of tiny pieces. Whole areas are still blank and if they are to become accessible must be worked upon by the most capable artisans, who are at the same time often the most

independent ones. With time, certain areas of knowledge are developed to a point where exciting patterns become visible and the gaps can be filled. The heightened effort of the last quarter-century has revealed large portions of the grand design. Proof has been found that a fundamental unity exists among the biological systems in most living things and that concurrent and coordinated research in biology and medicine is therefore essential. Many patrons, with quite different perceptions of need and opportunity, take a lively interest in influencing the distribution of labor and the resources applied to the pieces of the unfinished mosaic, but it must be added that these well-meaning efforts are nearly all concentrated at points of high clinical visibility—that is, they relate to the problems of human disease.

From the beginning, federal support—through NIH—has been categorical, that is, its interests have been subdivided principally into organ systems or diseases and administered by institutes bearing their names. These subdivisions have steadily increased over the years, partly because highly specific legislative mandates have resulted from political pressures on the Congress. Some more recent examples are those calling for intensified investigation, detection, and treatment of sickle-cell anemia, diabetes, arthritis, epilepsy, and orthopedic disabilities. In the early nineteen-seventies, legislation was passed that singled out cancer and cardiovascular, lung, and blood diseases to receive larger shares of the federal research budget. Indeed, provision was made for developing the budget for cancer studies independently of all other biomedical research. The impulse came primarily from outside the scientific establishment, though its proponents also included scientists and aficionados of science. The result was an unfortunate subordination of technical to political judgment or to emotion in the orchestration of the major biomedical-research efforts.

The effects have been mixed. There is no longer much question that the maximum utilizable funds are being devoted to research on cancer, a set of particularly dread and noxious diseases, that the quality of cancer research has risen, and that the vigor of the total research enterprise, whose expansion in constant dollars was leveling off prior to the National Cancer Act of 1971, is now being maintained. Moreover, a quality of "imbalance" is inherent in the support of research, for technical opportunities and needs are never evenly distributed.

There is a troublesome side, however, to this increased support: in only five years it has risen from about 17 per cent to 33 per cent of the annual NIH expenditure. Cancer research is by no means at a stage comparable to that supporting the engineering feat of placing a man on the moon. Knowledge is not yet adequate to "program" a certain decline in cancer mortality or morbidity, and viable leads are limited. Indeed, what we need to know could just as easily end up coming from research in some other, more basic disciplines whose support might well have been diminished because of budgetary constraints. Annual outlays for cancer research may soon reach \$1 billion and must increase at least \$100 million yearly just to keep pace with inflation at its current rate. At present the nation does not spend even half of that *increment* on population control, to give but one example for comparison. Attempts to accelerate research in this one quarter have perhaps been so vigorous as seriously to upset momentum of the general research movement. In the long run, the adjustment of support for research to retain the vitality of the whole is more desirable than is excessive dedication to one disease problem.

Interesting and controversial changes have also been made in the methods by

which public funds have been provided to biomedical researchers between 1950 and the present. Initially, nearly all NIH funds were awarded to individual scientists in institutions of higher learning to pursue their research ideas in operations of relatively small scale. These awards soon became the "project grant," an instrument of "free enterprise" the acquisition of which was dependent upon two important conditions: one was that it was subject to renewal in three to seven years; the other, that it pass the judgment of the researcher's own peers. Powerful sentiments and persuasive logic speak for maintaining the project-grant system as the primary vehicle for research support. Many important advances can be traced to the adaptation, extension, and successive refinement of discoveries supported by such grants. Indeed, there is little question that, if some disaster were to reduce biomedical-research expenditure to a fraction of its present level, the wisest course would be to commit it entirely to support in the form of project grants of the best and brightest scientists.

Over the years, NIH obligations to the traditional project grant have continued to increase, even allowing for inflation. The awards totaled \$327 million in fiscal 1965 and \$680 million in fiscal 1975 (\$393 million in constant dollars). Indeed, in any given year, a steady 10 per cent of the investigators thus supported are entering the system as grantees for the first time.

But the main increase in NIH support of research has been absorbed by larger units: the "program project" and the "center grant." These require the performing institutions to coordinate individual research projects in ways intended to enhance the national research effort more generally. However, the central, competitive, peer-review mechanism is still in operation for the components as well as the total of most of these operations, allowing individual initiative to survive even in these larger programs.

Another trend has been to increase the programming, or "targeting," of research. The desirability, and even inevitability, of this trend has escaped many of its detractors, who view the use of one of the instruments, the contract, as a steal from the traditional mode. The contract is often more useful than the grant in these highly focused activities; it is a tool, not an issue. Contracts constituted one-fifth of the \$1.9 billion awarded by all NIH for research and development in 1975. The major use of contracts has been for programs supporting cancer, heart, and lung research. In these and other areas, however, grants as well as contracts are now being applied increasingly to specific health problems. In this kind of programming, identification of the appropriate questions to be answered by the research is more important than the choice of funding device. The distinctive feature of the contract, in contrast to the grant, is that it throws greater responsibility for the details and strategy of the research concept on the staff of the supporting agency.

A corollary of both programming and aggregation is an increase in coordination among research centers. Both the information exchange and the competition that have resulted are no doubt beneficial to the acquisition of knowledge; but the consolidation of the research network may also have other effects on educational institutions, the consequences of which are not yet clear. Biomedical research will forever be intertwined with the educational process. Institutions of higher education continue to receive the major part of federal health-research funds—for example, about 70 per cent of all NIH awards in 1975. At the same time, medical schools conduct other research which is primarily designed to maintain the quality of teaching and which may be in conflict with the utilitarian approach to biomedical research that lies behind

the awarding of federal funds. This duality of interest is a potential source of conflict. The increasing sophistication and size of research operations and the growing demands for external coordination inevitably pull the medical-school scientist in one direction, while rising demands upon him for teaching and other services to his institution are pulling the other way. How the nation's medical schools will adjust to the current pressures for reform in the health-care system will have far-reaching effects upon how much, and how well, biomedical research will continue to be conducted in intimate relation to the education of physicians.

Between 1938 and 1972, the NIH contributed to the training of approximately 94,000 scientists, a number that constitutes a major part of the nation's biomedical-research personnel. Funding peaked in 1969, when obligations totaled \$168 million, and declined to about \$155 million in 1975. Meanwhile, support for research training had been phased out in most federal programs, while the administration in the previous five years had been questioning the NIH training programs with increasing intensity. On January 29, 1973, the president's budget proposed an abrupt termination of all new NIH training grants and fellowships, on the grounds that it was time to reduce a potential oversupply of scientific personnel. In addition, the awarding of fellowships solely to biochemists and clinical investigators was viewed as unfair discrimination against other disciplines. Members of Congress also thought it improper that some of the subsidized research trainees were subsequently turning to clinical practice for the sake of its much higher remuneration.

Fortunately for the biomedical research community, the cessation of training programs has been averted, at least until the issues can be better sorted out. As of 1975, the training authorities of the NIH and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) remain intact, though curtailed. Provisions are being instituted to recover the federal investment from any trainee who fails to remain in research, teaching, or other specified activities for a prescribed period. And the National Academy of Sciences has been commissioned to conduct annual studies to identify areas warranting future federal training support.

We lack information about the national pool of biomedical research personnel. In the present period of selective growth, roughly 3,000 new scientists are believed to be entering the profession each year. About two-thirds have received federal stipends for some stage of their training. The rate of turnover is uncertain, and the calculations are complicated by the changing roles scientists play in the system, depending upon their age and experience. That a continuous infusion of the young and talented is essential cannot be challenged. What is in question is the amount of financial risk and sacrifice that these individuals are willing to accept to enter and stay in research. An abrupt and complete termination of support would be a disastrous way to find the answer: determining research manpower needs will therefore be on the agenda for the coming decade.

As the nation's biomedical research programs have expanded, so has public interest in their conduct. Administration and congressional inquiries on the subject have tended to be addressed to the agency rather than to the discipline or the problem. Since the nineteen-fifties, the NIH has been examined by at least ten federal and non-federal commissions, most notably the Wooldridge Committee (1965),⁵ and the President's Biomedical Research Panel which reported in the spring of 1976. Congress has also conducted hearings. More recently, statutory mandates with time

and dollar limitations in designated areas reflect an extraordinary congressional interest in specifying the substance of certain programs.

The passage of broadened freedom-of-information legislation has exposed to public scrutiny most of the mechanisms for the research advisory process. Aside from threats to certain delicate aspects of peer review and to the still contested proprietary rights of scientists in their ideas, increasing public audit of biomedical research is generally salutary. It demonstrates clearly that research is susceptible to public direction and is in no sense the exclusive province of an unmanageable elite.

The "accountability" of biomedical research for the dysfunction of the present-day health-delivery system is difficult to assess. For the most part, research programs have been kept free of activities directed at regulation and delivery of health care. Attempts to reform health care through government intervention, however, have enlarged the several agencies of the Public Health Service. And debate has tended to clarify the point that NIH and ADAMHA, the principal federal supporters of medical research, are not *science* agencies but *health* agencies. ADAMHA combines missions of service and research. NIH has focused on its research mission, but has for years engaged periodically in "control" or "demonstration" activities designed to improve the translation of research findings into health practice. The relations between the research agencies and the health agencies of the federal government are poorly defined and are in need of periodic adjustment, particularly to ensure that health-service research and preventive activities are not neglected. Far greater discontinuities exist between the government and the private health sector; they have not yet achieved an entente capable of controlling some major deficiencies in health care.

While it is unlikely that biomedical research *per se* will produce further dramatic effects on, for example, infant mortality or the mean survival of those who have reached three score and ten years, it will continue to have considerable influence on decreasing premature death among those under age 65 and on improving health at all ages. These are not the only arguments, however, for retaining a powerful capacity to improve biomedical knowledge and its related technology. Biomedical advances are essential to the survival of the species. If we are to regulate our numbers in a rational way, we will have to control fertility by more effective biochemical or physiological methods than we now have. In the endless search for new sources of energy, food, and economic growth, we will continue to tamper with our ecology. Our ability to keep those environmental changes within the limits of human tolerance and adaptation will mean forever pushing forward the limits of our knowledge. Although the whole world will be at risk, it is the most affluent and advanced countries that must continue to bear the cost of such research and development.

In this perspective, the apparatus for effective conduct of biomedical research that has been created in North America, Western Europe, and the Soviet Union is a world resource. It must not be allowed to fall into disrepair, for once lost, it may well be impossible to replace. Furthermore, the "mosaic" of knowledge is becoming extraordinarily refined in certain areas. If continuation of the present pace is maintained, we will assuredly have a return on this investment in a mastery of most of the stubborn, chronic health problems we recognize today. In some respects, the growth of knowledge in biology and clinical research in the last decade alone has been breathtaking, and this momentum may be expected to increase if support is reasonably steady and wisely allocated, and if there is sufficient growth at least to accommodate young investigators and fresh ideas.

In the decades ahead, then, research will have to be carried out in a world made suddenly aware that its resources are finite and are shrinking under inexorable population pressures. For the developed nations, there may be an end to affluence; for developing nations, there may no longer be any hope of acquiring it. One need not subscribe totally to the bleakness of this vision to perceive that competition for resources of all kinds and at all levels is likely to intensify.

Some thought should therefore be given to the goals chosen for the decades ahead. Highest priority should not be given to the extension of the normal life span. There is little evidence that an even longer life means a better one, and a cure for aging is one of the least likely products of biomedical research. On the other hand, the aging process and its relation to diseases must be studied, for this approach offers promise of improving the quality of life. Limiting premature death, with maximum narrowing of current differences in life expectancy based on sex and race, should be given priority, as should minimizing the impact of physical and mental disability, and augmenting the positive aspects of health and well-being. Scientists must also supply the effective knowledge needed to make decisions in several critical areas of long-term social policy. These include efforts to provide a means for matching population levels with anticipated resources, to achieve the quality of environment sought, and to move toward a reduction of the burden of deleterious genes.

Finally, the scientific community must assume a greater degree of responsibility for the quality of the health care delivered, particularly by developing ways for applying research findings to the health-care system. This must include achieving consensus on what is ready and developing mechanisms for passing applicable findings from the community of research to that of health practice.

A corollary problem is presented by palliative technologies, such as renal dialysis, applied at exorbitant cost in present-day clinical settings. The mounting demands that these be extended to every patient in need of them suggests that science has some obligation to anticipate the fruits of its research, although it is not reasonable to expect inquiry to cease simply because it might lead to expensive therapies. A formula for compromise, incorporating both human and scientific values, is needed.

One of the perennial questions in biomedical science, particularly in public-policy discussions, is what constitutes an appropriate level of support. Philosophically, the question, How much research is enough?, has no objective answer. Subjective perceptions of its needs and opportunities must compete with assessments of needs and opportunities in other social areas. Yet, decisions on funding must be made.

The federal policy for the decade that began in 1956—that all meritorious research proposals should be funded—appears no longer to be feasible. Even at the time, the expansive policy attributable to HEW Secretary Folsom and endorsed by congressional action was only possible because of the relatively limited number of acceptable research proposals. Research support can probably never be increased rapidly enough to meet the infinite pressures generated by scientific opportunities, social needs, and public expectations. Yet it seems that any major advance in reducing disease and controlling health costs must derive from research; continued investment in research therefore becomes a *sine qua non* of public-health policy.

We are now at a plateau in federal biomedical-research support, during which increases will be modest and will not permit a significant expansion of the national enterprise. But what of the future? A breakthrough toward control of any one major disease might lead to a short-term spurt in research appropriations, with perhaps later

reductions or reallocations of funds to other areas. A major (or continuing) financial crisis for the government might depress prospects for research funding even at its present level in the decade ahead. If Congress takes a strong stand in support of its own overall budget ceilings, this might greatly reduce the competitive advantage now enjoyed by more popular federal programs including biomedical research. If national health insurance is adopted, this might strengthen the case for additional research, but it might also diminish research resources by making ever greater claims on the total health dollar. In the face of these unpredictables, the biomedical-research community would do well to propose a basis for setting some reasonable level of support. Perhaps the strongest case could be made for linking research expenditures to the cost of health problems to the nation, starting with the present ratio—about one dollar spent for every twenty-five of medical cost—and striving to maintain it.

The funding of health-related research by industry has grown erratically in recent years, increasing by about 5 per cent from 1969 to 1970 and about 9 per cent from 1974 to 1975. We can reasonably assume that there will be a modest expansion in constant dollars for the next few years, constituting a prudent investment in the development and testing of new and improved technologies for a steadily expanding world health market.

Private philanthropy has not quite kept pace with inflation in its support of health research. A decline in the share from private foundations has been largely compensated in recent years by voluntary-health-agency gains, but there is no reason to believe that private support can replace public support to any degree. The best hope is that a steady level (in constant dollars) of private funding will fill needs inadequately met by federal programs, provide seed money in areas where federal policy or public opinion inhibits federal support, and complement federal support in areas of common interest.

Research funding grows increasingly more unstable. In recent years, late appropriations have been further delayed by impoundment, release of impoundment, rescission, deferrals, and supplemental appropriations. One can learn to live on "continuing resolutions," but individual scientists and their institutions, not to speak of program managers, are ill-served by excessive uncertainties that may compromise continuity or lead to hasty commitments.

There are a number of possible ways to moderate these cyclical swings in the annual budget process, but no immediate prospect of implementing any of them. One would be to change from annual to multiple-year appropriations, with levels set for two, three, or five years ahead. But this is not likely to occur unless it is government-wide. However, if the Congress cannot meet its schedules under the new congressional budgeting act, such a change may be forced upon the system.

An alternative method would provide stable multi-year support for a basic core of research activity, with additional funds supplied through the annual appropriations process to handle special programs, such as expensive clinical trials. Through this system the predictable long-term needs of medical schools and other key institutions in the research process could reasonably be accommodated.

A third possibility is that of assigning an arbitrary support level for biomedical research (in constant dollars) for a specified period—say, five years—with that level determined by the activities under way at the time of decision, coupled with an assessment of additional opportunities and a frank exercise of bargaining power. The

level of funding could be set through the usual political and budgetary process, but should include a panel of experts providing advice. A survey on the Wooldridge model at the end of the first four years would assess the program issues (including how well the money was being spent) and provide recommendations for levels of support during the next five years.

If we could choose among these alternatives, we would not fail to improve conditions by opting for the first two- or three-year funding of the major enterprise, with compensation for rising costs and supplemental funding for projects of great promise. Periodic review of programs and needs conducted by experts through mechanisms ensuring objectivity and social responsiveness should be included.

A final problem, partly one of funding, partly of organization, concerns the distribution of appropriations for research. Is it preferable to concentrate such support in one or two agencies or to disburse it more widely throughout the executive branch of the government? Concentration provides visibility, which some contend would make budget cuts unpopular. It also permits the protection of vulnerable basic research by making its extension into application more obvious. On the other hand, diffusion of support provides for interagency competition, a healthy way to see that the public will is done, especially in areas of need that engender less professional enthusiasm.

It is this last consideration—how best to answer the needs of the public—that probably should prevail over a search for mere efficiency. And so it does. The organization of both the NIH and ADAMHA reflects the pragmatic orientation of this country (we are more interested in solving disease problems than in solving science problems) and the political strength of each of its categories—for diseases and disciplines both have political constituencies.

A new development that will affect the orientation of the health-research agencies and shift the boundaries between them and their sister federal health agencies concerned primarily with manpower, service, and regulation (Health Resources Administration, Health Services Administration, Food and Drug Administration, Communicable Disease Center) is the need to hold down federal health expenditures, driven upward by factors that not only increase the cost of health service but also expand the role of government as its purchaser. Where these costs can be laid to deficiencies in medical or psychiatric care, the biomedical and behavioral research communities must expand their activities to include more clinical trials of new interventions. The substantive issues here are scientific and technical, and the answers sought result from research. The scientific community cannot shun these practical responsibilities, nor would it be expedient for the government to create a "third force" to deal with this important dysfunction in the health system. There are many methodological problems in health-care delivery, however, for which answers, some of them extremely technological, must be found. Agencies other than the NIH and ADAMHA are equipped to deal with some of these problems, at least to a limited extent. Their competence should be strengthened and attached more closely to the other scientific forces; but health care will benefit by their retaining separate organizational identity and receiving separate appropriations.

We have all come to recognize another feature of health-care delivery which is not confined to America, nor, for that matter, to any social or political system. As the rate of change in technical content is increased by research and development, an intrinsic serial lag in response to change becomes more prominent, partly because the

delivery system is still relatively decentralized and unregulated. Some see a solution in combining research and health care. For example, there is a widely held belief that adequate treatment of certain forms of cancer can be obtained only in centers of cancer research. A large proportion of NIH support for cancer research is devoted to the establishment of these centers and to their extension into the community. This is laudable as an attempt to put research into practice and as a means of broadening access to the best health care. To the extent, however, that the health needs of today and tomorrow will be different, they cannot be served by a complete fusion of research and service. The goals are the same, but the processes and people involved are not. Understanding and preserving the differences will continue to be essential.

In ways that insist upon responsible performance and permit the achievement of difficult ambitions, the search for knowledge underlying man's physical and mental health must continue to be publicly supported and encouraged. It remains one of the brightest sources of light and hope for improvement in the quality of our lives and those of our children.

REFERENCES

- ¹J. W. Shannon, "The Advancement of Medical Research: A Twenty-Year View of the Role of the National Institutes of Health," *Journal of Medical Education*, 42 (February, 1967), pp. 97-108.
- ²*Basic Data Relating to the National Institutes of Health*, 1976, Division of Legislative Analysis, Office of Program Planning and Evaluation, NIH, February, 1976.
- ³*DHEW Obligations to Medical Schools, Fiscal Years 1967-69*, Division of Resources Analysis, Office of Program Planning and Evaluation, NIH, June, 1971. *DHEW Obligations to Institutions of Higher Education and Selected Non-Profit Organizations, Fiscal Years 1965-72*, Division of Resources Analysis, Office of Program Planning and Evaluation, NIH, December, 1974.
- ⁴Derived by Division of Resources Analysis, Office of Program Planning and Evaluation, NIH, from data maintained by the National Academy of Sciences and the Association of American Medical Colleges.
- ⁵D. E. Wooldridge, Chairman, NIH Study Committee, *Biomedical Science and Its Administration: A Study of the National Institutes of Health, Report to the President, February, 1965*, The White House (U.S. Government Printing Office, Washington, D.C. February, 1965).

OPENING REMARKS*

by

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Last May I gave several seminars at the Institute of Medicine on The Scientific Experience. I tried to put into words some things I felt about experimental science, especially in biology and medicine, and the immediate culture in which it flourishes.

I included an attempt to explain something of the discipline and the orthodoxy that hold researchers in the natural sciences together, the driving compulsion there is to find and to understand, and the stretches of tedium that sometimes extend for long times between discoveries.

A critical part of the game is the perception of asymmetry in observed phenomena and, then, the devising of ways to test the reproducibility of those deviations from randomness. After the phenomena are found to be real, there comes the construction of explanations. The degree to which these are synthesized to fundamental generalizations or get extrapolated to useful purposes determines much of the excitement and satisfaction.

The testing and the commenting on new stretches of intellectual fabric--as will occur here in the next day-and-a-half--is essential to the process, and no small part of the uncommon aesthetic experience that is science.

* Presented at "The Structural Basis of Regulation," a Symposium in Memory of Gordon Tomkins (1926-1975), National Institutes of Health, Bethesda, Maryland 20014.

It would be going too far to assume we have a corner on aesthetic experience, or on cerebral play. The heavy roles of perception, logic, and ego in science make stiff demands on the performers, however, and provide a consummate test for the right mix of certain human qualities.

There emerge from the endless, informal competition a few persons of rare qualities who will transcend their peers and form a locus of sustained intellectual excitement. Very occasionally one will also have the graces necessary to remain forever at the center of their affections.

In my mind, I can see Gordie Tomkins make a certain face at the suggestion this commentary might appear to be turning toward, making him the subject of a Helden Leben. With his exquisite sense of irony he would shake off the Wagnerian armor and distract us by pulling a pin on one of the imaginary hand grenades he used to toss into corners to demolish Phillistine uprisings or incursions by the Huns.

I think of him as a master of Metaphor, in Aristotle's meaning of the word: the ability to grasp the relationship between distant things.

In Science, creative movement depends heavily on this talent; and Gordon's agile leaps were unusually faster and often farther than anyone else's. Some of the larger concepts that emerged from his own thinking, and that he stimulated others to follow, will be among the threads of later discourse here.

Gordon's gift for metaphor spilled beyond biochemistry; however, into a sensitivity that made him an unforgettable companion. Any simple outing with him was likely to become an hilarious adventure. Even the briefest encounter with him left engrams and gestures that instantly gave away where you had been.

There was, too, an unselfconscious charm and sympathy that helped to make his manner absolutely infectious. The exposure to the infection also was likely to be prolonged; for Gordon was unselfish with his time and apparently distrustful of clocks.

It is now more than 25 years ago since I first met Gordon Tomkins. We were interns together at Peter Bent Brigham. The pay was free laundry, all one could eat, and the spirit-bonds that always exist among interns, who are like novices at some monstrous boot-camp.

As is probably true of all physicians, I remember more of that year than any since. Some of the brightest memories have Gordon in them. Like the muggy Saturday in that first July, when we had been sleepless for the requisite 100 hours. We went out to play tennis, and when we found we could only carry on from a sitting position, spent a half-hour in helpless laughter.

There was the time when the visiting expert dropped out of Grand Rounds and I was assigned to assemble some remarks in his place. Gordon instantly contrived a plan wherein I would appear in disguise as a specialist from Vienna. I often wonder how close I came to exile when he lost the false beard on the eve of my appearance.

As I remember it, we also both managed to get the mumps that year. Gordon gave me a red ribbon to tie around my waist. When his turn came, he needed it more than I.

If the Gods seemed cruel, then--and now, perhaps it is because they had given him gifts that were so much greater than the rest. To be in his company was our compensation, and we are each indescribably richer because he was one of us.

We are proud that Gordon's memory has unlimited residence here.
And it is a warming thing to have his colleagues and friends assemble
once again in his honor.

Thank you for giving me this chance to say what is in the heart of
all NIH.

STATEMENT OF DR. DONALD S. FREDRICKSON

Dr. FREDRICKSON. Mr. Chairman and members of the committee, although I have testified before this committee in 1967 and 1968 as Director of the Heart Institute, this is my first opportunity to appear before you as Director of the National Institutes of Health, a post which I assumed on July 1.

INTRODUCTION OF ASSOCIATES

This is also the first appearance of four new Institute Directors whom I should like to introduce:

Dr. Robert L. Levy became Director of the National Heart and Lung Institute in September. He joined the scientific staff of that Institute in 1963, shortly after receiving his M.D. degree from the Yale University Medical School, and for the past 2 years he has been in charge of the Institute's research programs on arteriosclerosis as head of its Division of Heart and Vascular Diseases.

Dr. Richard M. Krause joined the NIH, as Director of the National Institute of Allergy and Infectious Diseases, on September 24. He is a graduate of Case Western Reserve University School of Medicine and comes to us from Rockefeller University where he has been Professor and Senior Physician to the Hospital since 1968. His previous associations with NIH include service as Chairman of the Allergy and Im-

munology Study Section from 1966 to 1970 and as a member of NIAID's Infectious Disease Advisory Committee from 1970 to 1974.

Dr. David B. Scott returned to NIH on January 1 as Director of the National Institute of Dental Research. He first came to NIH in 1944, after receiving his D.D.S. degree from the University of Maryland, and he was one of the 13 people who comprised the staff of NIDR when that Institute was created, by act of Congress, in 1948. He left in 1965 to become a professor in both the school of dentistry and the school of medicine of Western Reserve University; since 1969 he has been dean of the school of dentistry of Case Western Reserve University.

I expect that the appointment of Dr. Robert N. Butler as Director of the National Institute on Aging will shortly be announced. After receiving his M.D. degree from Columbia University, he served as a research psychiatrist with the National Institute of Mental Health, which was then part of NIH, from 1955 to 1962. He has since then been in private practice here in Washington and has written three books and many articles on the problems of aging. He served as a consultant to the Senate Special Committee on Aging and, pending completion of the formalities concerning his appointment, he is now serving as a consultant to the Institute. Dr. Greulich, who has been Acting Director since July, will testify on the budget request but Dr. Butler will, of course, be glad to answer any questions you may wish to put to him.

BETTER DISSEMINATION OF RESEARCH RESULTS

Before dealing with the specifics of the budget request, I should like to respond briefly to some of the questions raised in this committee's report on fiscal year 1976 appropriations bill. The questions addressed to particular Institutes can be more effectively discussed with their directors later in these hearings but I should like to address myself to those that concern NIH as a whole. The most important of these is your request for a status report on our activities aimed at a better dissemination of research results. This is not only a matter that is of great concern in the Congress and elsewhere but it bears directly on the definition of the mission of NIH and the evolution of the role it must play in furthering the health of the American people.

Because of its immediate and continuing importance, I appointed, last September, a task force of knowledgeable scientists—under the chairmanship of Mr. Whaley, the Associate Director for Communications—to design, implement, and monitor this program. A subcommittee of professionals on this task force, chaired by Dr. Seal, the Scientific Director of the Allergy Institute, has accepted responsibility for a continuous review of research results to select those that are of potential importance to the practicing health professional and to assess their clinical significance. In addition, we have held informal consultations with outside communications experts and we have launched a series of national workshops to review existing means for disseminating research information and to recommend improvements and new approaches. These arrangements will, I think, provide a

sound basis for the orderly development of this program, for the continuing evaluation of its effectiveness, and for the identification of unmet needs.

INSTANT CONSULTATION

At last year's hearings, Dr. Lamont-Havers, who was then Acting Director of NIH, described the various kinds of research results and the groups to whom each type is of potential use. In this connection, he mentioned the lack of receptiveness, among some health practitioners, to efforts aimed at their continuing education but he affirmed NIH's determination to take all reasonable and feasible steps to make usable information as easily and readily available to them as possible. We have given much thought to how this can best be done and we have come to the conclusion that one effective approach is to create a system for instant consultation with someone knowledgeable about the state-of-the-art who would respond quickly and directly to a physician's need for information and advice. Such a system at the University of Alabama Medical Center at Birmingham—started in 1969 under the aegis of the regional medical program but now supported by State funds—is now used by three-quarters of the Alabama physicians outside the Birmingham area who each week make some 500 enquiries that are answered by the appropriate expert among the Center's 150 faculty members. We believe that this pattern can be followed with equal success in other areas and that some of the categorical research centers that NIH has established at major medical centers in various parts of the country provide a good foundation on which such a system can be built. To test the effectiveness of this approach, we are making arrangements to expand the Cancer Line service, established last year at the University of Wisconsin, so that it can provide a toll-free telephone consultation service for physicians throughout the State, on *all* disease problems. The success of this pilot project will, of course, depend—as it did in Alabama—on the enthusiasm and diligence of the professional staff in the Madison Medical Center. I have full confidence in their determination and ability to make it work and I expect that their efforts—and those of the dedicated group in Alabama—will set a precedent that other medical centers, with the assistance and encouragement of NIH, will be willing to follow. At the request of both the Alabama and the Wisconsin groups, we will organize a backup service, drawing on our experienced professional scientific staff in Bethesda, to deal with questions that the local faculty refers to us. I believe that direct links, between community physicians and their State or regional medical centers and between the centers and the NIH staff, dealing with real problems, as they arise, is probably the most effective way of bridging the gap between those at the research frontier and those at the bedside.

USE OF TELEVISION NETWORKS

In order to reach larger groups of health practitioners with more comprehensive reviews of the state-of-the-art in various fields of interest to them, we will, initially, use the existing State and regional special television networks that now link hospitals and medical centers in Indiana, South Carolina, the Houston area, the Dartmouth-Uni-

versity of Vermont area, the six-State WICHE (Western Interstate Compact for Higher Education) region, and the VA hospitals in Appalachia. The plan is to present regularly scheduled seminars, lectures, demonstrations, and other professionally oriented programs. The content of these programs must be of the highest quality and must be carefully tailored to the needs of an audience of busy practitioners. This takes time and is apt to be expensive but we will move as rapidly as talent and funds will allow. We expect that the audience for these programs can be substantially enlarged, and at a lower unit cost, through the use of the Communications Technology Satellite which was launched on January 17. NIH, through the Lister Hill Center of the National Library of Medicine—and in cooperation with the Health Resources Administration—is participating in the CTS project which, when it becomes operative next autumn, will provide two-way links between stations in Bethesda, Seattle, Fairbanks, Boise, Helena, Gainesville (Florida) and an NLM mobile unit. As these stations will be able to transmit, as well as receive, discussion programs will be possible. We also intend to make these facilities available, in time allocated to NIH, to professional societies which can, and must, play a more active role in the dissemination of information to the practicing community.

STATUS ON DISSEMINATION PROGRAM

A report on the status of the dissemination program has been submitted. A number of other activities are described therein, including the preparation of a monthly research review to be published in an established journal and an increased output of health information publications and audiovisual materials.

It is too early to respond to your request for "an assessment of the receptivity of those in the health care community to the various modes of communication". However, we are making arrangements with the American Academy of Family Physicians to conduct a survey among its members on the acceptability and effectiveness of the NIH dissemination activities. I can make a preliminary response to your request for an account of cooperation with other agencies. As I have already mentioned, we are collaborating with the Health Resources Administration on the CTS project. Information on NIH research has been regularly supplied to the new professional standards review organizations since last April, we are supplying videotaped lectures to VA hospitals, and we are working with the Bureau of Health Education, in the Center for Disease Control, on improving health education for the public. I must emphasize that cooperation with other Federal agencies—especially our sister agencies with the Public Health Service—is a two-way street: for the orderly conduct of the various Federal health programs, it is important that each agency recognize the responsibilities assigned to the others and cooperate with them in the execution of their mission while expecting and welcoming their cooperation in the execution of its own. In planning our dissemination program, we are alert to the mission of the Health Resources Administration in the education of health professionals, the responsibility of the professional standards review organizations for continuing education, and the expanded role of the new Bureau of Health Education for informing the public.

COOPERATION BETWEEN COMPONENTS OF NIH

Another aspect of cooperation and coordination that is of concern to this committee, as it is to me, is between the various components of NIH itself. All of us recognize, I think, that the categorical organization of NIH is efficient but is sometimes at odds with the natural distribution of labor among scientists converging, from many directions, on the solution of disease problems. The research scientist tackles biomedical problems from the point of view of the scientific disciplines in which he has been trained. A virologist, for example, is interested in identifying viruses and discovering what diseases they cause; his mental processes are not fenced in by the specific disease mission of the Institute that pays his salary or awards him a grant. It is therefore not surprising that most of the initial work on the virology of cancer was done by scientists supported by the Allergy Institute which has always been deeply involved in the study of viruses. The work of good scientists, in which intuition and curiosity must play a major role, often leads them into fields far removed from their own pastures. A recent example, with which you are probably familiar, was the development of the rubella vaccine which was properly the task of the Allergy Institute—which is responsible for infectious diseases—or, possibly, the Child Health Institute—which worries about the diseases of childhood and pregnant mothers—but the main work, the research that provided the breakthroughs necessary for the development of the vaccine was done, independently, by intramural scientists working in the Neurology Institute and in the Division of Biologics Standards, which was then part of NIH.

I mention these examples because I see the task of coordinating NIH activities not as that of a game warden trying to poach on the preserves of others but rather as that of a town crier who keeps everyone informed. The work of several institutes is often relevant to a particular diseases or medical problem—or, to put it the other way round, a particular disease often has aspects that fall within the purview of several institutes. This is particularly true for such areas of research as diabetes, cystic fibrosis, and most of the respiratory diseases. There is a limit, I believe, to the validity of concerns that a lack of coordination is retarding movement in certain diseases or that this is due to lack of management procedures that are effective for achieving engineering feats. Yet we cannot afford to ignore possibly better stimulants to creativity and the interactive acceleration of research. We will be most attentive to the request in the recent report of the Diabetes Commission and to other innovative ideas for creating more effective linkages between different laboratories and institutions working on common problems.

CONSTRUCTION PROJECTS BACKLOG

This committee has pointed out that NIH has a substantial backlog of construction projects, for which planning funds were appropriated in years past, and you have suggested that we review our needs and priorities and give you a status report on our present plans

and intentions. There are eight such projects with a total construction cost, at more or less current prices, of about \$260 million. This figure includes the two projects—the Lister Hill Building for the National Library of Medicine and the research facility for the Environmental Health Institute in North Carolina—for which provision was made in the vetoed fiscal year 1976 bill. The need for these two buildings can readily be justified but it is our considered view—based on extensive analyses and much discussion with the directors, the scientific directors, and the clinical directors of the various Bureau, institutes, and divisions—that an addition to the Clinical Center on the Bethesda campus must have a higher priority. This is partly because the problems that such an addition would solve are more urgent—they involve the care of patients—and partly because the proposed extension would serve the needs of at least nine of the Institutes. I am glad to say that the Secretary and the Office of Management and Budget with this assessment. The budget request now before you includes \$21.7 million for the first phase of its construction.

AMBULATORY CARE RESEARCH FACILITY

The proposed extension, for which the plans have been completed, is described as an ambulatory care research facility because it is primarily intended for clinical research involving outpatients who do not have to be hospitalized. This facility is designed to meet two critical needs. The first is to accommodate a shift in clinical practice and towards outpatient treatment and in clinical research toward the study of both of normal as well as diseased populations as outpatients. Impressive savings in the mounting costs of health care and in clinical investigation can be realized. No less important is the opportunity to extend knowledge about the development of disease, its diagnosis and treatment, in subjects living their lives at home or outside the artificial conditions of the hospital. Many clinical interventions must now be tested for their efficacy, safety, and cost-effectiveness in large numbers of subjects. Most important of all is the increased capability for research on the prevention of disease, the ultimate direction of all medical research. There has been a commendable shortening of hospitalization over the past several decades. The continuation of this trend has been made possible by numerous technical advances and has also, no doubt, been accelerated, in recent years, by the sharply rising cost of bed care. Many of the diagnostic procedures, for which people used to be hospitalized, can now be done—with greater convenience for the patient and at far less cost—on an outpatient basis. Similarly, it is now not only possible but preferable to give ambulatory care to patients in the early stages of chronic or degenerative diseases, during periods of remission, and in the recuperative phase of an acute illness. For research patients, the need for ambulatory care facilities has grown even more rapidly as the result of the expansion of research on normal human subjects and on illnesses, disabilities, or abnormalities that do not require hospitalization but that do require the use of the sophisticated

equipment and facilities of a hospital or large clinic. This is true of clinical research in general but is particularly true of the newer Institutes—Child Health, Eye, and Aging—whose research patients, for the most part, need not be confined to bed. As the result of all these factors, the Clinical Center now handles about 77,000 outpatient visits a year. This is an increase of 50 percent over 1971 and the figure would be very much higher if the present facilities were not now at capacity use. The number is already too high, leading to inconveniences for patients and some sacrifices of dignity, privacy, and the minimal comfort which they have a right to expect.

The Ambulatory care research facility will provide approximately 590,000 gross square feet of new space at a total cost of \$95 million. This will eventually accommodate over 190,000 outpatient visits a year—a capacity that will make it possible to expand clinical observations and trials and optimally to meet the foreseeable needs of future clinical research programs. In order to streamline the handling of outpatients, various technical services now located in scattered parts of the Clinical Center will be brought together in the new structure.

MODERNIZATION AND RENOVATION PROGRAMS

The other major, and even more urgent, need for which the new structure is required is to permit essential modernization and renovation of the existing structure. The Clinical Center was planned in 1948 and opened 22 years ago. What was once the most modern of American hospitals has suffered obsolescence in the succeeding years of great technological change. Facilities for certain types of surgery and intensive care are falling seriously below standard. Space for clinical pathology, diagnostic X-ray, and other new but essential diagnostic services is woefully inadequate. For purposes of renovation to the present Clinical Center \$8 million is included in the total estimated cost for the ambulatory care research facility. The proposed expansion and modernization of the Clinical Center is absolutely necessary if NIH is to remain at the forefront of the research activities required to continue its mission of providing the scientific basis for improving the health of the American people.

CONSTRUCTION BACKLOG STATUS

The status of the other items on the list of our construction backlog is as follows:

Construction of a research facility for the Child Health Institute can be postponed until the need for it can be reassessed after the addition to the Clinical Center is completed.

Plans for improving the master utilities on the Bethesda campus will also have to be revised in the light of changes made incidental to the construction of the Clinical Center addition.

The improvement and modernization of the NIH Animal Center at Poolesville, Md.—of which phase I has been completed—is desirable but not urgent. It may be that increased emphasis on clinical research

will lessen the demands made on our animal facilities but I do not want to predict that this will be the case.

The remaining item on the list is a building for the Fogarty International Center which was proposed before the large former residence on the NIH campus known as Stone House was refurbished and before the third wing of the general office building—building 31—was built. Stone House now has very attractive facilities for a limited number of scholars-in-residence and for moderate-size meetings and conferences. Building 31 now has a number of very large and well equipped conference rooms, one of which has facilities for simultaneous translation—a feature also included in the plans for the Fogarty Center building. I believe that the present needs of the Fogarty Center are adequately served by the facilities now available. The proposed new building would no doubt be useful—especially if the number of conferences held at NIH were to be increased—but it must, in present circumstances, be regarded as a luxury.

BUDGET REQUEST

The fiscal year 1977 budget request for NIH is just over \$2,165 million which is an increase of \$184.6 million over the President's revised budget for 1976—this is the level at which we are at present operating. The amount requested for fiscal year 1977 will meet all our major needs and will certainly enable us to maintain our high-quality research programs. It will not, of course, permit us to do everything we should like to do, or consider desirable, nor is it without problems but in view of this country's economic circumstances and the obvious need for budget restraints, I feel that OMB has dealt generously with medical research and that NIH has fared relatively well. I am also pleased to be able to tell you that NIH was allowed a freer hand in the allocation of its overall budget allowance than in the past few years. As a result, the distribution of the funds requested to the several NIH components and to their various activities represents our best professional judgment on relative opportunities and needs.

This year's budget makes a conscious and somewhat overdue effort to maintain capabilities and pursue selected important opportunities in the overall biomedical research effort. Since 1971, the year before the cancer conquest program was launched, the appropriation for the Cancer Institute has increased from \$233 million to roughly \$690 million in 1975 and 1976. That has been an appropriate surge of support for research on this disease problem, clearly identified—and, I think, properly so—as a national initiative. In 1971, funds for the Cancer Institute represented 14 percent of the total NIH appropriation; in 1975 and 1976 they represented 33 percent. The amount allocated to cancer in the fiscal year 1977 budget is 32 percent of the NIH total and to this must be added a substantial share of the separate appropriation for the construction of the Ambulatory Care Research Facility which will, proportionately, be of the greatest assistance to the Cancer Institute in carrying out its important mission.

The largest percentage increase (63.2 percent) has been allocated to the National Institute on Aging—an appropriation of \$26.2 million will enable this new Institute to mount a reasonable research program that will provide a sound beginning for the discharge of the mission for which it was created. The second largest percentage increase (35.6 percent) is for the Environmental Health Institute which has the unique responsibility, within the NIH family, for conducting research on a seemingly endless array of natural and manmade agents that assault our bodies and seem to cause a bewildering variety of diseases and disabilities. Many of these agents have not yet been identified and their relation to many diseases is still unsuspected or in doubt but we are clearly at the frontier of a new field in medical research that may prove as fruitful as the discovery, less than a century ago, that bacteria are a cause of disease. NIH must not shirk its responsibility for exploring this field but even with this increase the Environmental Health Institute will, in terms of budget, remain the smallest of the Institutes, other than Aging.

In order to achieve a better balance among the other programs to correct serious deficiencies, and to meet specific urgent needs, four of the Institutes and the Division of Research Resources have been allotted more modest but still substantial increases of 10 to 15 percent. The budget request:

- For General Medical Sciences is \$193.4 million, an increase of 15.5 percent;
- For Allergy it is \$135.6 million, an increase of 13.8 percent;
- For Heart & Lung it is \$342.9 million, an increase of 12.5 percent;
- For Arthritis it is \$180.8 million, an increase of 11.7 percent; and
- For Research Resources it is \$92.3 million, an increase of 10.8 percent.

For the remaining four Institutes—Neurology, Dental, Child Health, and Eye—the increases range from 8.4 percent to 5.7 percent which will maintain their programs at approximately their present levels.

The budget request for the Fogarty International Center includes an increase of \$2 million for its scholars-in-residence and fellowship programs, which are making significant contributions to the international exchange of information by giving outstanding foreign scientists an opportunity to work and study in this country and outstanding American scientists an opportunity to work and study abroad. For the Library of Medicine, an increase of \$6 million is requested, part of which will enable it to take full advantage of its participation in the Communications Technology Satellite project.

RESEARCH TRAINING

For research training, the budget request is \$105.1 million of which \$32.1 million is for the training grant programs that are being phased out. Of the remaining \$73 million, \$70 million is for fellowships under the National Research Training Act—an increase of \$14 million over

the fiscal year 1976 level. This amount will provide 2,396 fellowships of which 888 will be new awards.

Until the review of research grant applications is completed, it is not possible to say how many will be awarded to new investigators and how many to those who have previously had NIH grants. I share the concern expressed in the committee's report on last year's bill about the availability of funds for supporting new investigators and new ideas. On the other hand, I would also be concerned if support were to be denied an established scientist, engaged in a productive research project on which he has been working for many years, merely in order to make funds available for a newcomer who wants to pursue a new idea. Perhaps I can explain my ambivalence with an analogy: in politics, as in most fields, an infusion of new blood and new ideas is probably desirable but I would not want to vote against an incumbent, who has demonstrated his ability and is doing a good job, merely to make room for a newcomer. In both the laboratory and the legislature, it often takes many years to bring an idea to fruition or to achieve a goal. I have a strong conviction that the competence and industriousness of the investigator and the relevance and potential importance of the work on which he is engaged are the only criteria that NIH can properly use: the new must compete with the old and be judged, impartially, on the quality of their ideas and professional skills. The members of the NIH study sections are dedicated to the progress of research in the fields to which they have committed their own careers, they take their review task very seriously, and they are always eagerly on the lookout for worthwhile new ideas, new approaches and bright young scientists. I believe that, as a result of their efforts, the mix of old and new projects they recommend for support represents a fair judgment of the applicants and a prudent investment of public funds. The imposition of other criteria, not directly related to scientific merit and mission relevance, can only harm a system that has made the United States preeminent in biomedical research and has earned for NIH the respect of the scientific community both at home and abroad.

CONCLUSION

I am sure that the members of this committee share my hope that the effectiveness of NIH will continue to grow, that this country will march forward to greater achievements in research, and that the expectations of the American people for a longer, healthier life will thereby be progressively fulfilled—and that is the purpose for which the funds in this budget are requested.

DIRECTORS'S ADVISORY COMMITTEE
MEETING

February 9-10, 1976

OPENING REMARKS

by

Donald S. Fredrickson, M.D. 1/

I am delighted to welcome you here today to provide us with your perspective on a research activity of the National Institutes of Health that has broad public policy implications. This is a special meeting of the Advisory Committee to the Director of the National Institutes of Health. Current members of the Committee include Drs. Joseph Dodds, Roy Hudson, James Kelly, Robert Petersdorf, and Charles Sprague. In addition, I have invited a number of former Committee members as well as other scientific and public representatives to participate in this special session.

The purpose of the meeting is to seek your advice on proposed guidelines setting conditions for the conduct of certain experiments with recombinant DNA molecules that involve the introduction of foreign genes into bacteria. The promise of this research in improving understanding and possibly treatment of hereditary diseases, for example, is great. There is also a potential risk--that micro-organisms with transplanted genes might escape from the laboratory and infect human beings or animals, or alter the environment, and be dangerous or difficult to control.

1/ Director, National Institutes of Health, Bethesda, Maryland

Recombinant DNA research brings to the fore problems in public scrutiny of the process--and progress--of basic science. These experiments are extremely technical and complex--as I am sure you are aware from reading the background material sent you. This is a rapidly moving field, one of the leading edges of biological science. Molecular biologists in this research area have means of keeping informed, but even they may have difficulty in keeping abreast of the newest developments. It is no surprise that scientists in other fields and the general public have difficulty in understanding the advances in recombinant research. Yet it is vital that there be public awareness and understanding of this kind of experimentation. Its theoretical promises and perils have already been much discussed in the press but there is need for further informed discussion of the practical aspects.

It is important to recall that it was the scientists engaged in recombinant DNA research--among them Paul Berg, Maxine Singer, and David Hogness--who were involved in the call for a self-imposed moratorium, to assess the potential hazards and devise appropriate guidelines. Through their efforts the National Institutes of Health and the National Science Foundation supported the conference sponsored by the National Academy of Sciences held at Asilomar in February 1975. Their actions also led the NIH to establish an advisory committee to develop guidelines for recombinant research funded by the NIH, and to devise programs for assessing and controlling hazards in such research. This NIH committee has proposed the guidelines that we will be considering at this meeting.

There is precedent within the NIH for developing guidelines when research activity may place populations at risk. In clinical research, NIH guidelines have required informed consent of human subjects and an assessment, through mechanisms such as peer review and institutional review boards, of the risks and benefits of proposed research. Ethical, legal, and social values can thus be taken into account in fashioning the criteria and standards for clinical research.

The proposed guidelines on the DNA recombinant research emulate present NIH guidelines governing clinical research in that they represent an effort to balance scientific responsibility to the public and scientific freedom to pursue new knowledge. The public responsibility weighs especially heavy in this genetic research area. The scientific community must have the confidence of the public that the goals of this profoundly important research accord respect to important ethical, legal, and social values of our society. A key element in achieving--and maintaining--this public trust is for the scientific community to insure an openness and candor in its proceedings. Today's meeting and the Asilomar meeting reflect an intent of science to be an open community in considering the conduct of DNA experiments.

How to insure public and scientific participation in national science policy is a difficult problem--but not an insoluble one. Some attempts have been made in the legislature. Some have suggested a "science" court as a possible mechanism to air controversial science policy issues such as the one before us today. Its features would include (1) advocacy of

different opinions, (2) opportunity to cross examine witnesses, and (3) opinion based on a hearing record with statement of facts and reasoning in support of the opinion. This committee meeting is an alternative method to provide an airing of the issues, yet incorporating some of these features to assist us to reach a wise decision.

Your responses to the guidelines will assist in the task of defining scientific and public interests in the research involving recombinant DNA molecules. The original agenda, you will note, has been modified to allow more time for committee members to respond to or address questions to invited speakers as well as to public witnesses. Dr. Berg will begin with a discussion of developments leading to the call for a moratorium of certain recombinant DNA research; Dr. Stetten will review the work of the respective NIH committee; and Dr. Singer will describe the proposed NIH guidelines. Drs. Hogness and Curtiss, who are members of the NIH committee, will describe areas where there was disagreement in drafting the guidelines. When they have completed their brief reports, we will entertain questions the committee members may have for the speakers.

This afternoon there will be a film describing maximum containment facilities. This brings to our attention the important environmental impact concerns in recombinant research. Following a description of a recombinant DNA institutional review committee, we will open the discussion to the public as well as the committee. Questions will be entertained first from committee members and then from the public. There will then

be an opportunity for statements from public witnesses who have filed their statements in advance. Each witness will be allowed ten minutes. The committee members will have an opportunity to question each of the witnesses as time allows. Tomorrow, Dr. Stetten will present a summary of our discussions and then we will welcome response from the committee and public witnesses. In the last hour we will hear additional comments from committee members on the proposed guidelines.

In the next day and a half, I am especially interested that you, as the members of this committee, provide us with a sense of your comprehension of the nature of the experiments and the risk/benefit assessment. Further, your response to the proposed guidelines and procedural mechanisms for monitoring the research activity will be especially helpful. Seeing Judge Bazelon here today, I am reminded of a quotation from his friend, Justice Felix Frankfurter, who wrote, "The history of liberty has largely been the history of the observance of procedural safeguards." Procedural safeguards, with a full exploration of relevant facts and possible alternatives, must be the hallmark of this scientific process if we are to retain the trust and wholehearted support of society. That is the challenge before us today.

REMARKS

by

Donald S. Fredrickson, M.D.
Director
National Institutes of Health

at

Black History Week Ceremonies

Welcome to the fourth day of this year's Black History Week observance. I am very pleased to be a part of an organization such as the NIH which strives to foster the understanding and mutual appreciation of all races.

This year as we celebrate the Bicentennial, we must remain cognizant that our Black Americans have not enjoyed 200 years of freedom. Instead, they have braved what appeared to be unsurmountable odds to gain those inalienable rights guaranteed by the Constitution of the United States. Their past accomplishments have been many, and one can only admire their continued struggle to emerge as fully equal citizens of this country.

I have given my support to programs such as these which serve to point out the substantial role that our Black Americans have played in making this a great country, and as I have stated many times in the past, I am totally committed to equal employment opportunities and advancement for all at the NIH.

* Presented on February 12, 1976, at the National Institutes of Health, Bethesda, Maryland, in Building 1, Wilson Hall.

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American Society
for Microbiology

news



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Cover: Donald S. Fredrickson, Director of the National Institutes of Health. See article on page 266.

(Correction: The cover of the April issue illustrated "one of Leeuwenhoek's simple microscopes," as indicated in the legend. Regrettably, the legend also referred to "an instrument used by Koch." The latter was shown in the original photograph but was cropped out of the cover illustration. The News regrets the erroneous legend.)

FEATURE ARTICLES

The Impact of Biomedical Research on Health Care¹

DONALD S. FREDRICKSON

Director, National Institutes of Health, Bethesda, Maryland 20014

Health care today is one of the most complex of human endeavors. It involves all kinds of practitioners, diverse in their organization and modes of delivery, facilities of special design, and a constantly proliferating array of instruments, techniques, devices, and therapies. At the base of it all is biomedical research.

Medicine is still empirical enough; without research it would be medieval. We might still be relying on leeches and the purge, be resigned to periodic outbreaks of devastating plagues, and have to endure calamity with uncontrolled anxiety and pain.

The purpose of biomedical research is to improve the well-being of man through greater understanding of the nature of life. At the basic level, knowledge is generated about the functioning of biological systems and about the processes of growth, development, and decay. Resynthesis and development of this information leads to ways of understanding, preventing, treating, and curing disease.

Biomedical knowledge, like scientific knowledge generally, has been accumulating at an exponential rate, as reflected in the output of scientific literature. One sampling of biomedical

publications suggests an average annual increase in scientific papers of between 4 and 5% for each year from 1965 to 1973 (1).

It will take years to assess the impact of this avalanche of new knowledge, if indeed we can ever accurately measure it. In fact, one of our important tasks is to sharpen the tools for such measurement. Once gained, knowledge is added to a pool from which it can be drawn forever, and future applications cannot be foretold.

The results of biomedical research seem usually designed for the professional who delivers health care. They sharpen his skills and increase his armamentarium. Often research results become translated into social action, such as mass fluoridation, mandatory sanitation practices, and pollution control. Sometimes the individual can directly participate in research application, by changes in life style, for example, in improving nutrition and stopping smoking. When biomedical knowledge becomes a part of daily living, we tend to forget its origins in the processes of discovery and development.

Some claim can be made, of course, that the disappearance of smallpox should also mean an end to amortizing our debt to William

¹ Presented at the AAAS Meeting, Boston, Mass., 18 February 1976.

Jenner's experiments. The near end to measles and polio will soon make allusions to these achievements boring as well. But the benefits will march on through succeeding generations, while the fear and memory of the holocausts will disappear with time.

There are likewise overlapping claims to credit for the improved maternal and child care that have brought further decline in the infant death rate from 29.2 per 1,000 live births in 1950 to an estimated 16.5 in 1974. Over the same period, life expectancy at birth has increased by nearly 4 years.

Last year, for the first time since adequate statistics have been prepared, we had a decline in death rate from cardiovascular diseases. Just which of the discoveries leading to changes in treatment or prevention should have credit for this is not clear, but there is little question that better knowledge rather than chance was the major determinant. The outlook for other diseases has continued to improve, although the results are sometimes less dramatic. Research has had a revolutionary effect on life styles by making it possible for couples to plan the timing and number of their children. Moreover, an increasing number of serious defects are now detectable in utero, and safer abortion procedures allow parents an option of not having a child incapable of a reasonably normal life.

On the horizon are still more advances. The world is on the threshold of getting effective vaccines against hepatitis and better ones against influenza. New knowledge gained concerning the immune system and tissue compatibilities alone holds extraordinary promise of revealing innate tendency toward development of certain diseases.

Obviously, research is but one of the factors that have contributed to gains against mortality and morbidity. The knowledge had to be organized, applied, delivered—and both the public and private sectors were involved in these processes. Social and economic factors have also figured heavily in the advance in health status.

Recently, there has been an increasingly negative tone in economic analyses with reference to the impact of medical care on health status. Fingers are pointed at an asymptotic appearance to life expectancy curves. Another, more rational criticism is directed toward seeming inattention to accidents, homicide, and crime, which are more important than disease in determining death in youth. A serious disadvantage of such analyses is their inability to assess the benefits of medical care in terms of relief of disability, fear, or discomfort that can drastically change the quality

of life without appearing in the scores kept of mortality or productivity.

To a certain extent, the criticisms of medical care extend to a questioning of the value of continuing research. This is not anti-intellectualism but part of a national anxiety to commit public resources toward immediate social ends, rather than a long-term investment in acquiring useful information. This demand for some justification in economic terms of the return on research is fair but not always easy to satisfy.

In seeking to appraise the impact of research and technological development in general, economists have examined the factors that account for growth in national output. After allowing for such things as the number and quality of workers and the accumulation of capital, they have concluded that at least 30% of U.S. growth nationally has been the result of technological change. The average national economic rate of return for expenditures on R and D activities, which generate technical change, has been set at substantially more than 13% per year. This is a higher rate of return than the 10% per year associated with investment in a college education, for example. Historically the rate of return to capital investment generally has been much lower—in the range of 2 to 4%.

National agricultural research and development has returned between 35 and 170% per year, according to one reputable economist (2). The return from some trends of biomedical research may even exceed that range. A recent study of the economic impact of surgical research concluded that, in the single year of 1970, the United States had benefited to the extent of \$2.8 billion from a list of 16 surgical advances (3). The advances reduced death and disability from 20 disease conditions. The expenditure for the research that gave rise to those advances was but one-sixtieth of the benefit observed in the single year. The gains associated with the 20 conditions exceeded the entire national expenditure for all biomedical research in 1970. Since these gains not only continue but increase each year, it can be said that they alone "pay" in social terms for the entire national biomedical research effort each year.

The 60:1 ratio of benefit to cost in this case undoubtedly overstates the rate of return to investment in biomedical research generally.

All research is proposed with high hopes of significant application to human health, but the chain linking basic discovery to the patient is often long and indirect. Some research produces negative findings; hypotheses are discarded. Many experiments lead to no hy-

potheses. Many potential innovations prove unworkable or unmarketable. The gains from striking successes in research must, in an economic sense, "carry the cost" of blind alleys and modest achievements.

We have reason to believe that the impact of biomedical research on medical care is substantial. But it is difficult to prove and validate. The benefits from biomedical research reach deeply into personal lives and well-being. Moreover, they invariably affect many people and often the total population. Broad areas of effort should be set against broad areas of achievement, and benefit-cost comparisons must be calculated over a long span of time.

NIH is now engaged in a study of trends in the cost of disease since the turn of the century. We expect to be able to compare all biomedical R and D expenditures from 1900 to 1975, with gains observable in 1975 from the reduction in mortality, morbidity, and disability in all diseases over the 75-year period. We will consider prospects for the costs of ill health and of health care to the year 2000 as these reflect the changing demographic characteristics of the population, the growing proportion of the adult population to enter the labor force, and the slower economic growth to be expected as energy resources become more scarce.

One trend that must be taken into account is the strong disposition, everywhere evident in advanced societies, for the public to expect society to pay more of the costs of health care. This means the use of an ever larger share of national resources for health purposes. Several recent studies of trends in costs of health expenditures in countries of North America and Europe have shown, without exception, that the proportion of national resources devoted to health care in every country has been rising over the past decade regardless of the organization of the health care delivery system.

The trend toward rising health care expenditures in this country is unmistakable and widely publicized (4). Health care accounted for less than 5% of the Gross National Product (GNP) in 1940; today it accounts for 8.3%, and the likelihood is that it will rise to 10% in another 5 years and perhaps even higher in the future. This has little to do with changes in the state of American health (although the aging of the population is contributing to the rise). The upward drive essentially reflects public attitudes about the use of national income and the growing acceptance of a right to access to health care.

My purpose is not to debate the social issue. Rather it is to point out that, as a larger and larger share of our national resources is de-

voted to health care, the payoff to research that prevents or cures illness becomes great.

I have time here only to nod in the direction of a countervailing effect of research on costs. This is the inevitable creation of palliative technology as detours on the road to prevention. In the short run such costly developments tend to diminish the favorable economic impact of biomedical research on health care.

Constraints can be placed on government funding of R and D of inventions that may perhaps save the lives of only a few, with the costs distributed to many. I am personally prepared to consider seriously how one might arrive at such decisions. But I am very doubtful that we can settle on the goals—or correctly predict the outcomes of such an exercise.

Research gently but firmly pointed toward preventive modes is the long-run answer to ill health. It should not be curbed when other health costs expand but should expand at least at its historical rate of growth.

I noted earlier the evidence of growth of biomedical research at between 4 and 5% per year. This is very close to the growth that Derek De Solla Price observed for all fields of science as measured by number of scientific abstracts published, number of scientific journals, and number of new chemical compounds.

Scientific opportunity in the biomedical field will undoubtedly continue to grow with the accumulation of scientific knowledge. Science feeds on itself. There is no reason to believe that biomedicine will falter from lack of new opportunities for research in the future, although growth will be checked if resources for science are curtailed.

A recent study of the progress of discovery leading to the successful introduction of 25 biomedical innovations shows explicitly how the pace of progress depends upon adequate knowledge—not only in biomedical science but also in such other fields as computer technology, miniaturization of electronic circuitry, and material technology (5). Time after time developments were delayed until new knowledge became available (in biomedicine or another field) and enabled progress to be resumed. Among the 25 innovations, those that took the longest to move from the time work began on the final, successful idea to the time the innovations became generally available were in most instances held back by a lack of supporting technology. In contrast, work that moved expeditiously from time of conception to general availability always proceeded upon an adequate science base.

To keep this process going and to continue the current flow of new discovery and innova-

tion requires an appropriate level of federal funding of biomedical research. The following long-term considerations should be taken into account in setting the yearly level of federal funding:

1. The long-term economic gains from research and development expenditures are great and are destined to increase even more with the growing costs of health care.

2. Health expenditures in the United States have been growing at 5.4% per year, considerably faster than the real GNP (4.3% per year) and can be expected to continue to grow faster, at least in the near future.

3. Scientific opportunity, on the basis of historical trends, can be said to be growing at between 4 and 5% per year.

4. The ability of the economy to afford R and D—the national resource base—is expected to grow 4 to 5% each year.

5. If support for training is maintained, the supply of biomedical scientists available for research can keep pace with such growth over the next decade.

6. It is desirable to maintain a certain stability from year to year in biomedical research.

I believe that it would be desirable social policy to fund biomedical research at an annual level which, taking inflation into account, will maintain real growth at between 4 and 5% per year.

Whatever level of support is maintained, a fraction needs to be turned inward for continuing research on research itself. The system is itself subject to continuous change and is not ideal. The imperfections seem particularly apparent at the interface where biomedical research has its impact on health care. There is something still too informal about the collegial system for validation of applications and something too haphazard about methods for their distribution and continuing appraisal.

We have not mastered the creation of (intellectual) authority in reference to medical affairs. Indeed, being sensitive to the potential abuse, we have been loathe to experiment with new tyrannies, save for statistical ones in the conduct of vast clinical trials. Suffice it for now to acknowledge my awareness of other factors that determine health status. The oldest reform movement in town relative to the substance of health care, however, is still biomedical research.

References

1. The number of biomedical publications of 229 research institutions in the U.S. increased an average 4.6% per year between 1965 and 1973 (from 19,500 in 1965 to 28,000 in 1973) according to the progress report of Computer Horizons, Inc. on contract N01-OD-3-2109 dated 29 May 1975.
2. Griliches, Svi. 1964. Research expenditures, education, and the aggregate agricultural production function. *Am. Econ. Rev.*, December. Griliches has cited an unpublished Ph.D. thesis by Robert Evanson, "The Contribution of Agricultural Research and Extension to Agricultural Production." University of Chicago, 1968. as one of the studies pointing to relatively high (30-50%) rates of return on average to both public and private investments in research.
3. Surgery in the United States: a summary report of the study on surgical services for the United States, sponsored jointly by the American College of Surgeons and the American Surgical Association, Chapter X, Surgical research. 1975.
4. Health care expenditures are published annually in the Social Security Bulletin by the Office of Research and Statistics, Social Security Administration.
5. Analysis of selected biomedical research programs to the President's biomedical research panel, 31 January 1976 by Battelle Laboratories (final report on contract N01-PP-6-2104).

THE ROLE OF CONTROLLED THERAPEUTIC INVESTIGATIONS
IN THE NATION'S HEALTH PROGRAM*

Thank you for the opportunity to participate in this panel discussion.

INTRODUCTION

One year ago, the NIH began a major examination of its support of clinical trials, their impact and problems that must be considered in the support, initiation, and conduct of these activities. This examination led to the development of a better inventory of all NIH supported clinical trials and the establishment of permanent forum within the NIH to consider major issues in this area. We see some difficult and challenging problems ahead; some of which I would like to share with you this afternoon.

One of the most necessary and most difficult phases of biomedical research involves the demonstration, through the conduct of clinical trials, that an intervention in man is safe, practical and efficacious. Clinical investigation is tough.

There are many ways in which efficacy may be assessed ranging from clinical opinion to the most structured long-term experiments. Medical history has amply demonstrated that clinical opinion based on observation

*Presentation by Dr. Donald S. Fredrickson, Director, National Institutes of Health, at a panel discussion held by the American Association for the Advancement of Science, at their February 19, 1976, meeting in Boston, Massachusetts. The panel addressed "The Role of Controlled Therapeutic Investigations in the Nation's Health Program" and also participating in the panel discussion were Thomas Chalmers, President, Mt. Sinai University; J. Richard Crout, Director, Bureau of Drugs, FDA; and William Hubbard, President, The Upjohn Company.

is often insufficient and misleading approach to evaluating a procedure or a drug since personal bias may be a strong factor and a valid comparative group and adequate quantification are usually lacking. Nevertheless, there are circumstances where experience and observation have so narrowly defined the outcome of a disease (meningococcal meningitis) that no controls or only historical controls are necessary. At the other extreme is the randomized double-blind clinical trial, a prospective test of an hypothesis under the most objective conditions in which the precise identity of the test agent(s) is withheld from both observer and the subject. Especially, in chronic disease, where pathophysiology is often obscure and the clinical course so variable, the task of evaluating a new agent is difficult and the clinical trial must be particularly rigorous.

The Importance of Clinical Trials In General

- I. They are often the only means for testing and evaluating of new hypotheses.
- II. They can prevent premature introduction of interventions into practice.
- III. The outcome of clinical trials in the future will likely determine a more codified medical practice, which will, in turn, set the terms of reimbursement and standards of quality care.

NIH Support of Clinical Trials

I. Total Support (First sample last year.)

- a. Over 1,000 clinical trials each year at an annual cost of \$160 ('74) million (includes some preliminary phase-I studies);
- b. Includes all NIH trials--grant, contract, and intramural;
- c. Intramural trials--about 15% of dollar total;
- d. Total cost of 1,000 trials, from initiation to completion, approximately \$845 million.

But a poorly defined universe.
(New information coming this spring.)

II. Major Trials

Take our major Institute in terms of support of large trials--
NHLI support of clinical trials, 1964 - \$3.7 million, 1974 - \$40.6 million.

a. NHLI

- Five major trials--\$38.6 million in FY 1975.
- Estimated cost beyond FY 1975 for these five trials is \$184.9 million.
- Total population in the 5 trials is 41,200 individuals.

b. These five NHLI trials are:

1. Multiple Risk Factor Intervention Trial for Prevention of Coronary Heart Disease

- (a) Primary objective--to determine whether, for a group of men at above average risk of death from coronary heart disease, a special intervention program will result in a significant reduction in mortality from coronary heart disease.
 - (b) Start date--1972, duration--8 years.
 - (c) Support prior to 1975--\$ 25.8 million
1975 support -- 12.5 million
Projected beyond 1975-- 76.0 million
Total \$114.3 million
 - (d) Sample size--12,000
 - (e) Design--randomized, non-blind, fixed sample
2. Hypertension Detection and Follow-up Program
- (a) Primary objective--to determine the effectiveness of antihypertensive therapy in reducing morbidity and mortality from hypertension in a wide spectrum of persons with elevated blood pressure in 14 communities.
 - (b) Start date--1971, duration--11 years.
 - (c) Support prior to 1975--\$23.0 million
1975 support -- 11.1 million
Projected beyond 1975-- 42.5 million
Total \$76.6 million
 - (d) Sample size--11,000
 - (e) Design--randomized, non-blind, sequential

3. Lipid Research Clinics Prevention Trial

(a) Primary objective--to determine if reduction of cholesterol by drug therapy will significantly lower the atherosclerotic coronary heart disease rate in a group of hypercholesterolemic, but otherwise healthy men.

(b) Start date--1973, duration--8 years.

(c) Support prior to 1975--\$13.3 million

1975 support -- 8.8 million

Projected beyond 1975-- 46.2 million

Total \$68.3 million

(d) Sample size--4,000

(e) Design--randomized, double-blind, fixed sample

4. Aspirin Myocardial Infarction Study

(a) Primary objective--to determine whether the regular administration of aspirin to individuals who have had at least one documented myocardial infarction (MI) will result in a significant reduction in total mortality over the period of this trial.

(b) Start date--1974, duration--7 years.

(c) Support prior to 1975--\$ 0.0 million

1975 support -- 4.5 million

Projected beyond 1975-- 12.7 million

Total \$17.2 million

(d) Sample size--4,200

(e) Design--randomized, double-blind

5. Coronary Artery Surgery Trial

(a) Primary objective--to evaluate the long-term roles of coronary artery bypass surgery in the management of ischemic heart disease--to determine the morbidity and mortality in subgroups of patients with coronary artery disease treated by coronary bypass graft surgery and medical therapy compared with medical therapy alone.

(b) Start date--1973, duration--7 years.

(c) Support prior to 1975--\$ 1.0 million
1975 support -- 1.7 million
Projected beyond 1975-- 7.5 million
Total \$10.2 million

(d) Sample size--10,000

(e) Design--randomized, non-blind

c. Effect on NHLI in current year

1. Commits large proportion of budget and personnel for monitoring and review, limiting resources available for other programs.

FY 75 clinical trials \$39.9 million or 12.2% of total budget (\$328 million).

2. Contrast NCI, with very large resources--

FY 75 clinical trials \$36.4 million or 5.2% of total budget (\$699 million).

d. Future years--if overall budget fails to keep pace, continued support of major trials depletes funds for other programs.

III. Total NIH level

- a. No useful analytical approach to determining appropriate level of NIH investment in clinical trials.
- b. Level depends heavily on yield of investments in basic research and clinical investigations.
- c. Increasing NIH support of clinical trials reflects harvest of this investment.
- d. Awareness of responsibility.
- e. Must protect research base from erosion since basic research provides information critical to mounting clinical trials.
Not trivial question--secret locked away.

Major Problems

I would like to share with you some of the major issues which NIH is now facing in the support and conduct of clinical trials and invite your thoughts and advice on possible approaches as part of our deliberations.

I. Selection of the Question

- a. How do you determine the most important questions?
- b. Hangs on presence of adequate collective doubt on one hand, and collective agreement on the other.
 - 1. Collective doubt
 - (a) Many widely practiced therapeutic measures have enjoyed unquestioned exception for very long times:

95% of patients with localized disease are treated with surgery (usually radical mastectomy, particularly when axillary nodes are involved).

For patients with localized disease treated by surgery--survival has been unchanged in 30 years--yet only in recent years have surgeons begun to question this approach.

Surgery for breast cancer

In the mid-1800's, Charles Moore, an English surgeon, wrote a paper "On the Influence of Inadequate Operations on the Theory of Cancer"--advocated radical surgery including removal of axillary lymph nodes.

By the 20th century, radical mastectomy was regarded as the routine treatment for breast cancer confined to the breast and axillary nodes of same side.

Almost a century passed after the original thesis had been presented that challenges to this dogma appeared (in 40's).

Why?--radical surgery became so firmly established that few dared to question its role in managing patients with breast cancer.

- (b) In each physician, a touch of Falstaff that grows edgy at confrontation with uncertainty. Gratified with success of maneuver in small number of patients, he may momentarily lose patience and cry out:

"What, are thou mad? . . . Is not the truth the truth?"*

*Henry IV, part 1, act II, scene 4.

(c) Clinical trial--is an expression of uncertainty and acceptance of the fact that uncertainty can and must be evicted.

(d) Trial will proceed when enough collective doubt has been accumulated.

2. Collective agreement

(a) Knowledge base

(b) Significance of the problem

(c) Feasibility

(d) Potential benefit--difficult to assess cost/benefit

(e) "(a) through (d)" above most of which are as much ethical as scientific considerations.

c. The urge to do more trials has arisen with current rise in concern about the validation of current medical practice.

1. Trials also affect health care costs.

2. PSRO legislation raising public expectations--forces validation of established medical practice through conduct of trials to assess alternative standard remedies--resource requirements alone too great to support such approach--new treatments, rigorously evaluated will cause conventional ones to fade, as will heightening collective skepticism of medical community.

II. Clinical Trial Methodology

- a. Increasing critical evaluation of methodology in last two decades has improved our position.

Data Base

- 1. New epidemiological data on prevalence and incidence (Framingham).
 - 2. Biometricians have arrived to the rescue--benevolent tyranny of statisticians.
- b. The better circumscribed the question, the more likely is one to obtain an unequivocal answer (a tiny boat mismanaged goes down silently. When a large clinical trial goes down, it spills a vast cargo for all to see--UGDP study).
 - c. Assessment of minimum proofs necessary to accept or reject a hypothesis.
 - d. Need better identification and evaluation of end-points.
 - 1. Angina vs. "stone dead cold."
 - 2. Choriocarcinoma in women--prognosis (90% died) completely reversed when it was recognized that urinary chorionic gonadotrophin provided a much better end-point than disappearance of disease as determined clinically.
 - e. Need central mechanisms to keep track of clinical trials--so that we do not ask the same questions over and over again.
 - f. Examine and critique.

- g. Overall role of Federal government--FDA and its regulations.
Wise and flexible government standards/protection of the public interest.
- h. Data and safety monitoring.
 - 1. Importance to conduct of trial.
 - 2. Guarding public interest--must include representatives of consumers.
 - (a) NIH is attempting to develop reasonable standards for protection of participants.

III. Financing of Clinical Trials

- a. Clinical trials are expensive undertakings.
- b. Compelling arguments being made (by Dr. Chalmers)--with advent of some form of national health insurance, funds from such source should be provided to support clinical trials.
 - 1. Effectiveness and cost of care system ultimately will be determined by clinical trials.
 - 2. Remove clinical trials from competition with basic and clinical research programs--a factor which some say depresses number of trials conducted.
- c. Funds derived directly from health care system would likely require providers of care to determine the questions and contribute greatly to pressures advocating validation of established practices.

- d. Such a funding source would be sustained ultimately in economic terms, and thus over time, alter research mission of NIH.

IV. Freedom of Information Act:

- a. Data report and preliminary tabulations.
 - 1. Not exempt from disclosure provisions of Act at present.
(Nor can meetings to discuss same be closed to public.)
Public may obtain information on request.
- b. Impact of premature disclosure--
 - 1. Short-term effect may result in:
 - (a) Failure to reach successful conclusion.
 - (b) Early termination (decreased adherence to the protocol or to dropping out of the study--reduction in final number of participants--leading to adverse affect on investigator's ability to):
 - (1) define and detect differences among treatments.
 - (2) determine the magnitude of change between treated and control groups.
 - (3) measure the frequency of occurrence of the primary response variable in treated and control groups.
 - (c) May minimize the attainment of objectives and the applicability of the results or invalidate the results entirely.
 - (d) In double-blind randomized clinical trials--all of above plus blinded aspect of the study becomes extremely difficult to maintain--participant bias.

2. Long-term effects

- (a) Substantial loss or harm to society.
- (b) Significant financial loss.
- (c) Effectiveness (or non-effectiveness) of a treatment will not be established.
- (d) Suggestive preliminary results could be adopted by the health care system or remain unchallenged and unsubstantiated in the system for years.
- (e) Difficulty in launching another clinical trial to obtain a definitive result.

V. Compensation of Injured Research Subjects

- a. Harm to research subject (related to experimental design; not due to negligence)--no legal recourse for compensation.
- b. Issue raised by Tuskegee Panel, DHEW regs., National Research Act, and Commission for Protection of Human Research Subjects.
- c. The issue: Is society morally obligated to compensate participants injured in the course of research which it has mandated?

One may argue--volunteer abrogates right to compensation by his act; in some circumstances, he may even benefit.

- d. DHEW examining this very complex issue.

In Closing

Clinical trials are indispensable. They will continue to be an ordeal. They lack glamour, they strain our resources and patience, and they protract the moment of truth to excruciating limits. Still, they

are among the most challenging tests of science and medicine. I have no doubt that when the problem is well chosen and the study is appropriately designed, and that when all the populations concerned are made completely aware of the route and the goal, the rewards are commensurate with the effort. I have no doubt that we have made significant strides in planning and conducting clinical trials in the last two decades. This momentum can carry us to new levels in the future, and the problems of today will serve as markers to a course that is well-charted. If clinical trials ultimately will determine the effectiveness of health care, and the alternative is to pay the costs of perpetual uncertainty, have we really any choice?

UGDP

Duration 14 years (1961-1975); 1,000 patients; \$107

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Statement by Director, National Institutes of Health

on

1977 Appropriation Estimates

Mr. Chairman and Members of the Committee:

Although I have testified before this Committee in 1967 and 1968 as Director of the Heart Institute, this is my first opportunity to appear before you as Director of the National Institutes of Health, a post which I assumed on July 1.

This is also the first appearance of four new Institute Directors whom I should like to introduce:

... Dr. Robert I. Levy became Director of the National Heart and Lung Institute in September. He joined the scientific staff of that Institute in 1963, shortly after receiving his MD degree from the Yale University Medical School, and for the past two years he has been in charge of the Institute's research programs on arteriosclerosis as head of its Division of Heart and Vascular Diseases.

... Dr. Richard M. Krause joined the NIH, as Director of the National Institute of Allergy and Infectious Diseases, on September 24. He is a graduate of Case Western Reserve University School of Medicine and comes to us from Rockefeller University where he has been Professor and Senior Physician to the Hospital since 1968. His previous associations with NIE include service as chairman of the Allergy and Immunology Study Section from 1966 to 1970 and as a member of NIAID's Infectious Disease Advisory Committee from 1970 to 1974.

... Dr. David B. Scott returned to NIH on January 1 as Director of the National Institute of Dental Research. He first came to NIH in 1944, after receiving his DDS degree from the University of Maryland, and he was one of the 13 people who comprised the staff of NIDR when that Institute was created, by act of Congress, in 1948. He left in 1965 to become a professor in both the School of Dentistry and the School of Medicine of Western Reserve University; since 1969 he has been Dean of the School of Dentistry of Case Western Reserve University.

... I expect that the appointment of Dr. Robert N. Butler as Director of the National Institute on Aging will shortly be announced. After receiving his MD degree from Columbia University, he served as a research psychiatrist with the National Institute of Mental Health, which was then part of NIH, from 1955 to 1962. He has since then been in private practice here in Washington and has written three books and many articles on the problems of aging. He served as a consultant to the Senate Special Committee on Aging and, pending completion of the formalities concerning his appointment, he is now serving as a consultant to the Institute. Dr. Greulich, who has been Acting Director since July, will testify on the budget request but Dr. Butler will, of course, be glad to answer any questions you may wish to put to him.

I found, on returning to NIH after a year's absence, that the morale of the staff is excellent and that both the intramural and extramural activities are being pursued with vigor, enthusiasm and imagination. There are some problems such as the retention of highly skilled staff against an increasing gradient of compensation available in other Federal and private medical sectors, the need to define the mission of NIH and the boundaries of its activities in the light of increasing concern about the costs of health

care, and the essentiality of sustaining the search for basic knowledge while increasing its clinical application toward prevention and cure of the many disease problems still to be solved.

One of the major problems is to define what needs to be done to ensure an adequate linkage between biomedical research and the delivery of health services and to determine what role NIH can, and should, play in bridging the gap -- for I have no doubt that a gap does exist. By this I do not mean that research results are lying on the shelf unused -- this is, I know, a common allegation for which, however, there is simply no evidence. It is not a lag in development, but premature application of inadequately tested technology that is sometimes a problem in the linkage of research to health care. The continued success not only of NIH but of the biomedical research capability in this country which NIH sustains will, I think, depend on finding ways to meet the demonstrable needs of the health care system without, at the same time, damaging or subverting the research effort on which future progress in improving our health care capabilities so clearly depends. In its larger sense, it is not a problem which NIH can solve alone. The bridge across the translation gap will have to be built from both ends -- and it will require consistent and innovative approaches at both ends. My main concern, as Director of NIH, is to consider what can best be done from the research end.

We are exploring what needs to be done to meet the needs for more clinical investigations, which are required to translate research done in the laboratory and with animals to medical problems of humans. There is increasing need for more carefully designed large-scale clinical trials to confirm the effectiveness of and demonstrate new diagnostic or therapeutic procedures.

Another aspect of the translation gap is perceived as the problem of the dissemination of research results to the health service community. The better dissemination of research results is a matter that is not only of great concern in the Congress and elsewhere but that bears directly on the definition of the mission of NIH and the evolution of the role it must play in furthering the health of the American people.

Because of its immediate and continuing importance, I appointed, last September, a Task Force of knowledgeable scientists -- under the chairmanship of Mr. Whaley, the Associate Director for Communications -- to design, implement and monitor our communications efforts. A subcommittee of professionals on this Task Force, chaired by Dr. Seal, the Scientific Director of the Allergy and Infectious Disease Institute, has accepted responsibility for a continuous review of research results to select those that are of potential importance to the practicing health professional and to assess their clinical significance. In addition, we have held informal consultations with outside communications experts and we have launched a series of national workshops to review existing means for disseminating research information and to recommend improvements and new approaches. These arrangements will, I think, provide a sound basis for the orderly development of this program, for the continuing evaluation of its effectiveness, and for the identification of unmet needs.

At last year's hearings, Dr. Lamont-Havers, who was then Acting Director of NIH, described various kinds of research results and identified groups to whom each type is of potential use. In this connection, he mentioned the ever-increasing uses for continuing education of health practitioners. He affirmed NIH's determination to take all reasonable and feasible steps to

make usable information as easily and readily available to them as possible. We have given much thought to how this can best be done and believe that one effective approach is to improve systems for 'instant consultation' with physicians in need of information and advice. Such a system at the University of Alabama Medical Center at Birmingham -- started in 1969 under the aegis of the Regional Medical Program but now supported by State funds -- is now used by three-quarters of the Alabama physicians outside the Birmingham area who each week make some 500 enquiries that are answered by the appropriate expert among the Center's 150 faculty members. We believe that this pattern can be followed with equal success in other areas and that some of the categorical research centers that NIH has established at major medical centers in various parts of the country provide a good foundation on which such a system can be built. To test the effectiveness of this approach, we are making arrangements to expand the 'Cancer Line' service, established last year at the University of Wisconsin, so that it can provide a toll-free telephonic consultation service for physicians throughout the State, on all disease problems. The success of this pilot project will, of course, depend -- as it did in Alabama -- on the enthusiasm and diligence of the professional staff in the Madison Medical Center. I have full confidence in their determination and ability to make it work and I expect that their efforts -- and those of the dedicated group in Alabama -- will set a precedent that other medical centers, with the assistance and encouragement of NIH, will be willing to follow. At the request of both the Alabama and the Wisconsin groups, we will organize a back-up service, drawing on our experienced professional scientific staff in Bethesda, to deal with questions that the local faculty refers to us. I believe that direct links,

between community physicians and their State or regional medical centers and between the centers and the NIH staff, dealing with real problems, as they arise, is probably the most effective way of bridging the gap between those at the research frontier and those at the bedside.

In order to reach larger groups of health practitioners with more comprehensive reviews of the state-of-the-art in various fields of interest to them, we will, initially, use the existing State and regional special television networks that now link hospitals and medical centers in Indiana, South Carolina, the Houston area, the Dartmouth-University of Vermont area, the six-State WICHE (Western Interstate Commission for Higher Education) region, and the VA hospitals in Appalachia. The plan is to present regularly scheduled seminars, lectures, demonstrations and other professionally oriented programs. The content of these programs must be of the highest quality and must be carefully tailored to the needs of an audience of busy practitioners. This takes time and is apt to be expensive but we will move as rapidly as talent and funds will allow. We expect that the audience for these programs can be substantially enlarged, and at a lower unit cost, through the use of the Communications Technology Satellite which was launched on January 17. NIH, through the Lister Hill Center of the National Library of Medicine -- and in cooperation with the Health Resources Administration -- is participating in the CTS project which, when it becomes operative next autumn, will provide two-way links between stations in Bethesda, Seattle, Fairbanks, Boise, Helena, Gainesville (Florida) and an NLM mobile unit. As these stations will be able to transmit, as well as receive, discussion programs will be possible. We also intend to make these facilities available, in time allocated to NIH, to professional societies which can, and must,

play a more active role in the dissemination of information to the practicing community.

A report on the status of the dissemination program has been submitted. A number of other activities are described therein, including the preparation of a monthly research review to be published in an established journal and an increased output of health information publications and audio-visual materials.

In order to assess the receptivity of those in the health care community to the various modes of communication, we are making arrangements with the American Academy of Family Physicians to conduct a survey among its members on the acceptability and effectiveness of the NIE dissemination activities.

As I have already mentioned, we are collaborating with the Health Resources Administration on the CTS project. Information on NIE research has been regularly supplied to the new Professional Standards Review Organizations since last April, we are supplying video-taped lectures to VA hospitals, and we are working with the Bureau of Health Education, in the Center for Disease Control, on improving health education for the public. In planning our dissemination program, we are alert to the mission of the Health Resources Administration in the education of health professionals, the responsibility of the Professional Standards Review Organizations for continuing education, and the expanded role of the new Bureau of Health Education for informing the public.

Another aspect of cooperation and coordination that is of concern to this Committee, as it is to me, is between the various components of NIE itself. All of us recognize, I think that the categorical organization of

NIE is efficient but is sometimes at odds with the natural distribution of labor among scientists converging, from many directions, on the solution of disease problems. The research scientist tackles biomedical problems from the point-of-view of the scientific disciplines in which he has been trained. A virologist, for example, is interested in identifying viruses and discovering what diseases they cause; his mental processes are not fenced in by the specific disease mission of the Institute that pays his salary or awards him a grant. It is therefore not surprising that most of the initial work on the virology of cancer was done by scientists supported by the Allergy Institute which has always been deeply involved in the study of viruses. The work of good scientists, in which intuition and curiosity must play a major role, often leads them into fields far removed from their own pastures. A recent example, with which you are probably familiar, was the development of the rubella vaccine which was properly the task of the Allergy Institute (which is responsible for infectious diseases) or, possibly, the Child Health Institute (which worries about the diseases of childhood and pregnant mothers) -- but the main work, the research that provided the 'breakthroughs' necessary for the development of the vaccine was done, independently, by intramural scientists working in the Neurology Institute and in the Division of Biologics Standards, which was then part of NIE.

The work of several Institutes is often relevant to a particular disease or medical problem -- or, to put it the other way round, a particular disease often has aspects that fall within the purview of several Institutes. This is particularly true for such areas of research as diabetes, cystic fibrosis, and most of the respiratory diseases. There is a limit, I believe, to the validity of concerns that a lack of coordination is retarding movement

in certain diseases or that this is due to lack of management procedures that are effective for achieving engineering feats. Yet we cannot afford to ignore possibly better stimulants to creativity and the interactive acceleration of research. We will be most attentive to the requests in the recent report of the Diabetes Commission and to other innovative ideas for creating more effective linkages between different laboratories and institutions working on common problems.

The budget request now before you includes \$21.7 million for the first phase of the construction of the addition to the Clinical Center on the Bethesda campus. The proposed extension, for which the plans have been completed, is an Ambulatory Care Research Facility primarily intended for clinical research involving out-patients who do not have to be hospitalized. This Facility will serve at least nine of the Institutes and is designed to meet two critical needs. The first is to accommodate a shift in clinical practice toward out-patient treatment and in clinical research toward the study of both normal as well as diseased populations as out-patients. Impressive savings in the mounting costs of health care and in clinical investigation can be realized. No less important is the opportunity to extend knowledge about the development of disease, its diagnosis and treatment, in subjects living their lives at home or outside the artificial conditions of the hospital. Many clinical interventions must now be tested for their efficacy, safety and cost-effectiveness in large numbers of subjects. Most important of all is the increased capability for research on the prevention of disease, the ultimate direction of all medical research. There has been a commendable shortening of hospitalization over the past several decades. The continuation of this trend has been made possible by numerous technical advances and

has also, no doubt, been accelerated, in recent years, by the sharply rising cost of bed-care. Many of the diagnostic procedures, for which people used to be hospitalized, can now be done -- with greater convenience for the patient and at far less cost -- on an out-patient basis. Similarly, it is now not only possible but preferable to give ambulatory care to patients in the early stages of chronic or degenerative diseases, during periods of remission, and in the recuperative phase of an acute illness. For research patients, the need for ambulatory care facilities has grown even more rapidly as the result of the expansion of research on normal human subjects and on illnesses, disabilities or abnormalities that do not require hospitalization but that do require the use of the sophisticated equipment and facilities of a hospital or large clinic. This is true of clinical research in general but is particularly true of the newer Institutes -- Child Health, Eye and Aging -- whose research patients, for the most part, need not be confined to bed. As the result of all these factors, the Clinical Center now handles about 77,000 out-patient visits a year. This is an increase of 50% over 1971 and the figure would be very much higher if the present facilities were not now at capacity use. The number is already too high, leading to inconveniences for patients and some sacrifices of their dignity, privacy and comfort.

The new facility will eventually accommodate over 190,000 out-patient visits a year -- a capacity that will make it possible to expand clinical observations and trials and optimally to meet the foreseeable needs of future clinical research programs. In order to streamline the handling of out-patients, various technical services now located in scattered parts of the Clinical Center will be brought together in the new structure.

The other major, and even more urgent, need for which the new structure is required is to permit essential modernization and renovation of the existing structure. The Clinical Center was planned in 1948 and opened 22 years ago. What was once the most modern of American hospitals has suffered obsolescence in the succeeding years of great technological change. Facilities for certain types of surgery and intensive care are falling seriously below standard. Space for clinical pathology, diagnostic x-ray and other new but essential diagnostic services is woefully inadequate. For purposes of renovation to the present Clinical Center \$8 million is included in the total estimated cost for the Ambulatory Care Research Facility. The proposed expansion and modernization of the Clinical Center is absolutely necessary if NIH is to remain at the forefront of the research activities required to continue its mission of providing the scientific basis for improving the health of the American people.

This year's budget makes a conscious and somewhat overdue effort to maintain capabilities and pursue selected important opportunities in the overall biomedical research effort. Since 1971, the year before the Cancer Conquest Program was launched, the appropriation for the Cancer Institute has increased from \$233 million to \$762 million in 1976. That has been an appropriate surge of support for research on this disease problem, clearly identified -- and, I think, properly so -- as a national initiative. In 1971, funds for the Cancer Institute represented 14 percent of the total NIH appropriation; in 1975 and 1976 they represented 33 percent. The amount allocated to Cancer in the FY 1977 budget is 32 percent of the NIH total and to this must be added a substantial share of the separate appropriation for the construction of the Ambulatory Care Research Facility which will, proportionately, be of the greatest assistance to the Cancer Institute in carrying out its important mission.

The FY 1977 budget request for NIH is just over \$2,165 million which is \$137 million less than the FY 1976 appropriations that were passed over the President's veto last month. This decrease is due to the fact that the FY 1977 budget was constructed on a lower base, before the FY 1976 appropriations were enacted; it does not reflect \$112.5 million of the FY 1976 Congressional increases for the Cancer, Heart, Child Health, and Aging Institutes, \$43 million for General Research Support Grants, and \$51 million in non-recurring construction funds.

For the other NIH components, there are increases totalling \$42 million which represent our best professional judgment on relative opportunities and needs. This amount includes \$6.8 million for the National Institute on Aging which, with an appropriation of \$26.2 million, will be able to mount a reasonable research program that will provide a sound beginning for the discharge of the mission for which it was created. There is an increase of \$8.4 million for the Environmental Health Institute which has the unique responsibility, within the NIH family, for conducting research on a seemingly endless array of natural and man-made agents that assault our bodies and seem to cause a bewildering variety of diseases and disabilities. Many of these agents have not yet been identified and their relation to many diseases is still unsuspected or in doubt but we are clearly at the frontier of a new field in medical research that may prove as fruitful as the discovery, less than a century ago, that bacteria are a cause of disease. NIH must not shirk its responsibility for exploring this field but even with this increase the Environmental Health Institute will, in terms of budget, remain the smallest of the Institutes, other than Aging.

In order to achieve a better balance among the other programs, to correct serious deficiencies, and to meet specific urgent needs, there are increases of \$8.5 million for the Allergy Institute, \$6 million for the General Medical Sciences Institute, \$1.8 million for the Neurology Institute, and \$1 million for the Arthritis Institute.

The budget request for the Fogarty International Center includes an increase of \$1.8 million for its scholars-in-residence and fellowship programs, which are making significant contributions to the international exchange of information by giving outstanding foreign scientists an opportunity to work and study in this country and outstanding American scientists an opportunity to work and study abroad. For the Library of Medicine, an increase of \$6 million is requested, part of which will enable it to take full advantage of its participation in the Communications Technology Satellite project.

For research training, the budget request of \$108.5 million of which \$34.1 million is for the training grant programs that have been superceded by the fellowships awarded under the National Research Training Act. Although this Act has expired, we still have authority for the old training and fellowship programs that are being phased out. Funds totalling \$73.2 million for fellowships under the National Research Training Act are included in the budget submission in the expectation that the renewal legislation, which is now in conference, will be enacted before this Committee acts on the FY 1977 appropriation. The amount requested for these new fellowships represents an increase of \$19.5 million which will provide for about 900 additional fellowships.

I am sure that the members of this Committee share my hope that the effectiveness of NIH will continue to grow, that this country will march

forward to greater achievements in research, and that the expectations of the American people for a longer, healthier life will thereby be progressively fulfilled. That is the purpose for which the funds in this budget are requested.

THE NEW BIOLOGY AND SOCIETY*

by

Donald S. Fredrickson, M.D.**

I. Science and the State

A. The Narrow Internal Ethic of Science

Some of you may recently have seen the television show in which James Watson (author of the Double Helix), Crick, Pauling, and others discussed frankly the events leading to the awarding of the Nobel Prize to Watson and Crick for the working out of the structure of DNA.

Here was a demonstration of high science as practiced at one classical extreme...a secretive highly competitive gamble for high stakes...the pursuit of intellectual status in a game of priority in which the only thing worse than being wrong is being second.

There have been a number of commentaries on the institution of science and the behavior of scientists - though few views from the inside as

* Presented at the Alpha Omega Alpha Lecture at the Mount Sinai School of Medicine, New York, New York, on March 3, 1976.

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frank as Watson's. Haberer wrote a useful book called Public and the Community of Science, published in 1969. He seizes on Rene Descartes, the great materialist and mathematician, for example.

The ultra-Cartesian model of scientific behavior has at least three aspects pertinent to my discussion today..

One of these we can note and dismiss as typical of creative temperament in general. This is the rivalry or the competition inherent in intellectual achievement. We may be appalled to note how Newton and Leibnitz brought forth the calculus in utter disdain of each other. Or how that patron saint of free inquiry, Galileo, ignored the works of Copernicus. The two Marks - Twain and Rothko - were not easy artists, Celini could be disgusting, Joyce impossible, and Robert Frost unbearable, in the same kind of agony for identity.

Another Cartesian attribute, while not unique to, is more representative of science. This is an absolute faith in the power of reason and an unremitting pursuit of truth - revealed, that is by reproducible experimentation - as loftier by far than any other preoccupation. This is not free of a taint of exaltation, a rise to

omniscience. Think of Oppenheimer's flash of kinship with the "demigods of reason" at the instant of the burst of awful light over Almagordo.

Descartes practiced and taught a third rule of scientific behavior - that of shunning of public commitment. There may be an element of omniscience in this. It is derived, however, more from fear of distraction, of loss of precious time and energy to social causes less amenable to pure reason. In it, too, is a suspicion of the Social Order as uninterested, or antagonistic to the sacred right of free inquiry.

Thus, those two 17th century founders of the institution of science began the policy of "prudential acquiescence." This cautious approach to first the Church, then the State as permitters, or later as patrons, of Science has marked the history of Science until contemporary times.

The rising power of modern science and its prodigious spawn of technology has changed of late its relationship to the state. There is more than ever the dependency upon public patronage. But there is developing a sharing of power and responsibility that neither Bacon or Descartes could have foreseen.

The turning point was the Second World War. Out of this came the dramatic spurt in growth of biomedical science. But it was not here - but in atomic physics - that the proponents of science and technology found common cause with the makers of destruction. Prudential Acquiescence became Shared Power and so it must continue, for the genie cannot be put back in the bottle.

And during the formation of this uneasy detente, there emerged among the participating scientists, one or two of the old Cartesian qualities, but more importantly, a repudiation of the withdrawal from societal commitment. (You are perhaps too young to know of the bitter personal rivalries between Oppenheimer and Teller and Lawrence...but you are aware that the social control of peaceful use of radiation is a reasonably working one. It could not be so if scientists had shunned their public commitment.)

It was with good reason that I began my talk today with a vignette featuring biological scientists. What elements of that play may have been somewhat distasteful I can readily excuse. For I regard the Machievellian overtones of "The Double Helix" as reflecting more than anything else as the heat of the engine of creation - a byproduct of the intellectual drive that often

leads to extraordinary achievement. Its bad manners are excusable because only a few, playing at the same game - and not the public interest - may be injured.

More importantly, the example is useful because it involves the substance of a New Power that has come of late to biology. And the beginnings of this have seen another refutation of Cartesian withdrawal. Another need for Science to share a new power with society in an exquisitely responsible manner has come upon us.

This time it is Biology and the Healers who must do no harm.

II. The New Biology

A. Historical

1. Evolution has preceded within species - because natural barriers exist to production of hybrid creature like Sphinx, minotaur and chimera (head of lion, body of goat, tail of serpent) (per Stanley Cohen).

2. Always been some limited exchange between bacterial species through recombinations of DNA.

(Maxine Slide 1)

3. In late 1960's & 70's series of independent discoveries occurred (so called "plasmid engineering")

DNA ligases

a. methods for breaking and joining DNA molecules from different sources

Restriction endonucleases (Eco RI)

b. a suitable gene carrier capable of replicating itself and foreign DNA joined to it.

plasmids ("R factors")

c. means of introducing the recombinant DNA into a host cell

certain salts

tests: foreign nucleotide sequence

d. methods for cloning for cells with particular recombinant.

4. Complications Foreseen

a. Workers recognized potential benefits

1) genetic knowledge

a) mapping

b) expression control

2) possible production of useful products

3) possible beneficial transformations of plants, among other hosts.

b. AND potential hazards in transformed hosts,

1) if indiscriminate transformations practical without proper safeguards.

2) if antibiotic-resistant strains released

B. Asilomar

1. 1973 - Gordon Conference

letter of Singer/Soll

2. 1974 - Committee on Recombinant DNA Molecules

Paul Berg

3. Feb 1975 - Asilomar Conference Center

86 + 15

a. voluntary moratorium

b. call for guidelines

4. NIH committee assembled and met the day after Asilomar

• An expression of excitement tempered with a high sense of moral responsibility.

• Its task within reason because controls are feasible, in light of modern genetic knowledge.

• Consider in a few examples how difficult are the decisions.

(Slides 2-6)

NIH Committee

- a. A task of matching unknown hazards against speculative benefits
- b. A growing consensus of agreement to err on conservative side/placing in jeopardy opportunity for certain participants to continue their line of experimentation-- though not apparently hazardous.
- c. Anxiety and concerns of curbs on freedom of inquiry tempered some by realization
 - 1) despite construction of number of recombinants in which eukaryote DNA was incorporated into probaryote hosts--no evidence of eukaryote DNA expression
 - 2) Safer vectors were being obtained with promise of permitting further advance
 - 3) Reasoned mode of procedure for developing guidelines based on estimate of total hazard as

Likelihood of spill x Consequent Damage
(Physical x Biological Containment)

C. The Guidelines

1. Presented to

- a. Committee Composition
- b. Technical Experts
- c. Public
 - 1) professionals
 - 2) environmentalists

(Slides 7-14)

2. Comments and Deliberations

- a. How can you establish proper policy in reviewing technology (control of science)?
 - What is effective public participation?
(Kennedy complaints on Asilomar)
- b. Who has Burden of Proof?
 - 1) The Scientist to show no risk?
 - 2) The public to show risk?
- c. What about the Risk of not going forward under proper safeguards?
- d. Decision to proceed "is a moral issue", has been said

Weight of Argument was to proceed, but cautiously.

We have done so in regard to

- 1) infectious materials
- 2) radioactivity
- 3) toxic chemicals

Possibly the ultimate morality in regard to the unknown is the style of procedure.

D. The Style of Procedure

1. Firm but Evolvable Guides
2. Technical training
3. A combination of control (NIH) and Peripheral (Institutional and Investigator) Responsibilities

E. Extension of Controls

1. Beyond federal experiments--
 - a. to industry
 - b. to rest of the world (Ashby Committee)
2. To restriction enzymes as used in schools, elsewhere
3. Extension to Law?

III. The New Biology

Sinsheimer: In the advent of a new biological research, the research process is changing from one of analysis to one of synthesis (true already of much of technology that has been easier to contain and some with more obvious individual benefits--like artificial kidney). The complications are great. The process is an irreversible one. Here, vectors will escape and there will be no (perfect) control.

The Two Ethics of Science

The test now is the relative strengths of the "institutional ethic" of science and its "methodological ethic".

The meaning of this is that science has dealt very well with the construction of an internal set of rules, which guard its processes against fraud or violation of strict evidentiary codes, and assure interactions among professionals that facilitate and enable the pursuit of truth or knowledge of the universe. As essential as this "methodological ethic" is, or at least as successful as it has been in fostering discovery in the natural sciences, it is bound to lead to conflict between science and externalities. Science is a risk venture dependent upon non-scientists for support. Science must impress and convince externally, for it cannot consume its own products as a source of power to continue. And there is the almost irresistible urge to push back the boundary of the unknown.

It is the "institutional ethic" of science that must guide it in informing society of the purposes or intent of science and of the implications of its

technology, and in assuming that share of responsibility for the external decisions that bear on the well-being of science and public alike. The wisdom, skill and morality with which science assists society in these translations is, in effect, its institutional ethic.

The emergence of a New Biology introduces a note of special urgency into the construction of a stronger "institutional ethic." Biomedical Research is already caught up in a reform movement dealing with a shifting frame of reference concerning medical ethics and human experimentation, including fetal research.

In regard to clinical investigation, the U.S. is among the most advanced in the direction of governmental regulation.

Comes now an issue in regulation of basic research, a problem which the State alone, without the full cooperation of Science cannot successfully manage.

The Institution of Science moves further from the stage of "prudential acquiescence" to "Responsible power," guiding the state voluntarily to its regulation.

To the extent that biomedical science is a humanitarian institution it will remain among the most favored of social causes. But this now means that the joyful search for truth (knowledge) is linked to an awesome and increasing responsibility.

STATEMENT

by

Donald S. Fredrickson, M.D.
Director, National Institutes of Health

at the
PRESS CONFERENCE

First Results from the Diabetic Retinopathy Study--
A Nationwide Clinical Trial of Photocoagulation Therapy

Today the National Eye Institute is announcing the results of a most important clinical trial which has reached a conclusion about a scientific hypothesis in the management of diabetic retinopathy.

It is noteworthy that the results are being discussed before the trial is scheduled to end. This briefing is a reflection of our belief that it is important that such trials be monitored constantly and as soon as the data permit a conclusion, that it be made known. Decisions can then be made on the basis of that information for the benefit of participants in the trial as well as for all who have the condition being studied.

The NIH is strongly committed to engaging in the type of study being reported today. It is one of a large number of clinical trials which we are now conducting or supporting at a substantial investment for NIH (about ten percent of our total research budget). At this time we have underway 31 major trials each involving more than 1,000 randomized subjects at a cost of \$33.2 millions in FY 75. These trials involve approximately 175,000 patients and in total will cost \$345 million.

* Held April 1, 1976 at the National Institutes of Health, Bethesda, Maryland 20014.

Such trials are absolutely essential for evaluating new findings from fundamental and clinical research prior to their dissemination throughout the medical care system and for validating existing medical practices.

One of our primary policy concerns is to develop a means for a more structured approach to the selection of questions for clinical trials. We also recognize the need to develop greater skill in devising our approach to scientific testing on questions that bear on medical care techniques.

Remarks for Dedication of Health Sciences Library
University of Virginia*

Donald S. Fredrickson, M.D.**

Thomas Jefferson would find himself in congenial company on this occasion. Mr. Jefferson believed in libraries.

In this lovely springtime in Washington, D.C., many thousands of visitors are thronging through a great library, to the side of which stands the Supreme Court Building and to the front of which stands the Capitol. Visitors are being told once again that it was Mr. Jefferson's personal library that formed the basis for that huge library--the Library of Congress.

And in 1825--the year before Mr. Jefferson's death--his granddaughter, Virginia Randolph, set about preparing an inventory of 700 books--the library for the then-new University of Virginia. She listed 91 titles in "anatomy and surgery" and 238 titles in "medicine."

It was these books--nearly half the original University Library--that formed the beginning for this Health Sciences Library. These first medical books had been bought at Mr. Jefferson's request.

Despite his skeptical views on much of the therapy of his time--skepticism which now we can only applaud--he believed that the teaching of medicine and human biology was properly a university function. It was

*Delivered on April 9, 1976

**Director, National Institutes of Health

almost 100 years later that the controversial and influential Flexner report echoed the Jeffersonian view and advocated its logical complement-- that medicine should only be taught in an academic setting.

It is in that spirit that we celebrate a noteworthy event in the distinguished history of this institution. Every important constructive step like this one has a rich history of unrecognized individual effort. The Virginia Medical Alumni, friends of the University, and other local sources who contributed substantially to the cost of the construction of the Health Sciences Library can view the completed task with satisfaction. They have had a part in giving new strength to a vital instructional and research arm of the University. The Federal and the Commonwealth governments can feel confident that they have made wise use of the public funds here invested.

Investment in medical education and research is indeed a prudent use of public funds. Though students of the University and citizens of the Commonwealth will primarily use the Library, the benefits will often reach far out into the world and touch the lives of people who have no idea of the place in which we are assembled. Consider as just one example of the potential outreach of any place of training and scholarship. . . your own distinguished alumnus, Walter Reed. The very success of his work has obliterated our sense of its importance. Yet less than a century ago, the city of Memphis, Tennessee, was left a ghost town by a visit of yellow fever.

The memory of the man has survived that of what he did. And it is fitting to note here that shortly before he died, he was Director of the great collection which later became the National Library of Medicine. The Director of this unique institution, a part of the NIH family, Dr. Martin Cummings, accompanied me here today for this celebration.

Having a personal commitment to research, I am moved on this occasion to reflect on the discrepancy that exists between the sometime image and the real role of a library in the process of gaining new knowledge. The caricature is that of a lifeless archive, where facts are shrouded in language and their external sleep guarded by signs calling for Silence. In reality, the library is the restless, ever-expanding processor of a stream of information fed from countless sources. It is the collective memory of all who have lived since thoughts and observations were recorded in written form. And as the center of information flow, the library is the "steersman" or Kuvernos, the Greek root from which Wiener plucked his term "cybernetics," the theory that information is control.

If it was even possible for Leonardo da Vinci, he clearly was the last scientist to recapitulate by his own experiments and imagination the sum of knowledge in any field. But there is something more about the process of recording and describing scientific endeavor. If it has not entered the collective memory, it has not--in a real existential sense--ever occurred. The slogan "publish or perish" taught by researchers to their apprentices should be phrased "publish to exist." Such, then, is the power of the record.

There is something awesome about the dependency we have come to have upon these deceptively peaceful-looking institutions called libraries. Even their growth is embarrassing.

The Health Sciences Library we dedicate today is in itself measure of the expansion of knowledge. In its first century the medical collection grew about twentyfold from the 300 original volumes. By 1960 the collection had grown to 55,000. Since that time it has more than doubled.

This measure does not reflect the constant inflow of information through the 1,500 scientific journals and other periodicals to which you have access here.

The library cannot grow or function, however, in the absence of its surrounding university. The mere gathering and storing of staggering amounts of information is not enough. There is a requirement for sifting and re-synthesis. In much the same way as the multiple areas of association of the cortex of the brain must do, the users of the library must filter and assimilate the shower of incoming sensory information before it merges it into the reservoir of useful experience.

Almost 20 years ago, K. G. Saiyaidain, then India's Secretary of Education, described the process of information assimilation in a lecture at Columbia in words which apply aptly to the process of health professional education and research. He said, "It is a long and arduous journey from Information which is the lowly foundation of knowledge, to vision which is its highest fruit. Through the impact of personal experience,

information assumes the role of knowledge, but even when knowledge comes, wisdom often lingers far behind . . . It is only when knowledge has been passed into judgment and becomes assimilated into good behavior that wisdom is born. And when wisdom is welcomed into the sanctuary of the heart and becomes wedded into emotions it puts on the mantle of charity and compassion."

Alfred North Whitehead put it more economically, "A merely well-informed man is the most useless bore on God's Green Earth."

While both of these expressions concerned the individual, they are, in essence, equally applicable to a scientific community as a whole. Society hopes and expects that the information derived from research will indeed be transformed not only into knowledge, but also into compassionate care and better health.

There is growing public interest in making sure that the fruits of research are applied promptly and universally as better measures for the diagnosis, treatment, or prevention of disease.

Occasionally we get questions from members of Congress which indicate that some of them believe that research findings--"cures" for important disease problems are gathering dust on a laboratory shelf somewhere because scientists have neglected to make them known. While all the motivations and mores of the research community assure the reporting of such findings, we must be alert to the possibility that gaps in communication can develop, and that the best and latest is in fact not universally practiced.

The NIH has been directed by the Congress to improve the dissemination of information from the research it supports. Currently such research results annually in the publication of some 35,000 reported findings--of which an overwhelming number represent incremental bits of knowledge which are useful in the process of research itself. The number of findings ready for application to patient care is relatively small.

Communication within the scientific community is reasonably effective. To a certain extent this internal exchange is much concerned with conveying information. Conversion of scientific information to knowledge useful to the physician or other health professional or into wisdom useful to the public is something we do less well.

We need to find ways to strengthen the collegial processes whereby we decide whether something is worth adding to medical care or preventive practice. We need to convey those decisions more clearly and completely to all who may benefit.

Sometimes we are asked why NIH does not send out "the latest word" in regular bulletins that might set the algorithm of medical practice to be followed all over the land. As a center of communication, there may be ways in which we can quicken the pulse of information exchange. But the fountainhead of all knowledge on health is not located in the transplanted pool of Bethesda. We are part of a great network of academic medical centers and other seekers of knowledge spread across the land

and beyond the oceans. Nearly 90 percent of the research carried out by or through NIH takes place elsewhere--at centers like the University of Virginia.

When we discuss Federal responsibility for determining and making known what is the latest and best we inevitably involve the 150 or so centers where most of the action is.

Once, in a less complicated time, the President of the United States served as a principal communicator of research-derived medical information of great consequence.

When Harvard professor of medicine Benjamin Waterhouse learned of Jenner's use of cowpox pustules for vaccination against smallpox, he immediately sent for some of the material. After successfully vaccinating his children and servants in July 1800, Waterhouse promptly notified Mr. Jefferson, then Vice President, of Jenner's discovery. The always inquisitive Jefferson at once arranged for vaccination of his household and shortly thereafter as President used his influence to establish the procedure in Philadelphia and other cities throughout the country.

One of the primary purposes of this Library is to serve as a resource for practicing health professionals in the Commonwealth, as well as for the alumni of the University of Virginia. This service is only one facet of the Center's emphasis on continuing education.

Like most academic medical centers, the University of Virginia is assuming greater responsibility for helping its graduates to keep abreast. But assuring that every physician and every nurse in its sphere of influence knows and practices the "latest and best" is probably a greater challenge for an academic center than its primary task of training students. The ability of an institution to motivate its graduates to continue their education on a lifelong basis is a true index of its excellence.

Whitehead compressed into one sentence a comment on the role of teaching, of the library and of motivation. He observed: "So far as the mere imparting of information is concerned, no university has had any justification for existence since the popularization of printing in the fifteenth century."

Methods for continuing education have gone far beyond the use of printed materials and the lecture. There is a growing array of ingenious methods for conveying information to busy, distracted practitioners--by audio cassettes, video tapes, information juke boxes, television conferencing, and satellites. Useful as it may be, however, communications technology cannot substitute for the unsatisfied appetite of the mind. Coupled with directed curiosity the tools supplied by a facility like the Virginia Health Sciences Library can make it possible for today's student in the health professions as well as those in active practice to be armed with the latest and best and continuously to replenish the armamentarium.

It seems to me an intriguing practicality to have constructed this library over a city street. It completes my earlier search for symbolism of the library in the main stream of traffic. The decision by the Charlottesville City Council to make the first grant of air rights for construction of a library is comfortably Jeffersonian.

I have added a sufficient increment of words in dedication of a House designed to contain more memorable ones. / Let me in closing remind you of a distraught librarian at Yale who became aware of the large number of local gentry who stopped on the street to admire the new library. The librarian charged outside to the steps in front of the building and startled the passersby with the irritated shout, "What you see is not the Sterling Library--the Sterling Library is within!" And so shall it be with this library. Its very existence begins not with construction or ceremonies of dedication--but with its use.

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DETERMINANTS OF HEALTH STATUS*

Donald S. Fredrickson, M.D.**

I am sorry that Lewis Thomas could not be here. This is not the first time that I have come in for him as designated hitter. But he never loans me his bat. On this occasion I've barely had the time to get the signs from the manager.

It is for this reason that I am grateful, as I know you are too, to the editors of the program for the provision of so eclectic a choice of background papers on the range of current policy questions related to health care.

A central theme dominates all but one of these papers-- cost. If cost was not an issue, would we have any "health policy" problems? Of course we would, but the policy questions would be very different.

So perhaps it is fair to suggest that the topic of the session is rather less the Determinants of Health Status than the cost implications of those determinants. The determinants are somewhat academic in themselves. One seems to plunge into the real world in dealing with their costs. I accept that challenge. Yet, I will need to add my impression that the simple cost accounting of health requires you to submerge persons into populations. And there are real limits to this kind of abstraction.

*Presented at the National Leadership Conference on America's Health Policy, Washington, D.C., April 29, 1976.

**Director, National Institutes of Health, U.S. Dept. of Health, Education and Welfare, Bethesda, Maryland.

Walter has told you what he thinks determines health status, we don't disagree. I'd say the determinants are 3 or 4, in the main. There is "life style"--note the discussions by Boudreau and by Meenan in the program. There is "environment"; it has taken on enormous significance. And then there is the medical aspect of health status. It subdivides into at least two broad sub-categories--human biology and the delivery of medical services.

Malfunctions in these four areas are the blocks to Utopian health status. One can grapple with the defects in a variety of holds. The strongest is knowledge. Being, by Presidential choice with consent of the Senate, a principal keeper of the lamp that lights a way toward revelations, I suppose its natural that I want to focus on--research, and particularly upon biomedical and behavioral research in relation to health status, and its cost implications.

To begin with, I am inevitably biased. I hope to argue rationally, but certainly not dispassionately.

In the years since the end of the second world war the Federal Government has invested a great deal of money in biomedical research. The annual appropriation of the NIH has now passed \$2 billion a year. Public patronage has been generous. And I think, in the main, it has been wisely given and carefully administered. In purchasing power, the resources for research have begun to level out, however, both here and abroad.

The total health bill of the country has passed \$115 billion a year and shows no signs of levelling off. As you are aware, or certainly will be by the end of these two days, the costs are truly staggering. The problem is not peculiarly American, but is similar in all of the major western (and at least some eastern) European countries.

The problem is critical. So much so that it may breed uncritical responses. It has been suggested that research, or its spawn, "technology" has been a significant factor in runaway health costs and that if the research or the technology could be curtailed, then one aspect of the continual cost increase would also be controlled. Gaus' paper in the program does not explicitly present such a point of view, but suggests it.

This, I submit, is a lopsided assessment of the problem. Fully adequate economic analyses of issues related to health status and health care are in a deplorably primitive stage. In general, they have broken down cost increases into two factors, increases in price (inflationary increases) and increases in service (or increases in the use of resources). Increases in population, of course, also require more services. Thus, if the cost of x-raying a broken arm doubled between 1950 and 1970, that was a price increase. If the accepted view of treatment in 1950 called for one x-ray, but the approach in 1970 called for two x-rays, each at the same

price as in 1950, that doubling would represent an increased use of resources, or an increased use of medical goods and services. The increased use of resources includes changes in technology and changes which result from research.

The Social Security Administration reports that from 1950 to 1975 health expenditures increased from \$12 billion to \$118.5 billion. It concludes that 48% of the increase was attributable to price inflation, 15% to population growth, and 37% to a residual set of factors including technological changes.

The residual cost increases include such things as the increased use of in-patient hospital care rather than out-patient care, the use of more, and more expensive, drugs, the increased use of laboratory tests, the increased use of more highly specialized and skilled medical personnel, and the increased use of expensive technologies of which renal dialysis (or the artificial kidney) is a frequently cited one, but only one among many.

Costing out the impact of research is very difficult. The increased use of laboratory tests, for example, results in part from the fact that more good, useful tests are available. It also reflects the increased need to practice "defensive medicine". The latter is obviously not the fault of research.

Let us turn to treatments. Take renal dialysis, for example. Dialysis was first used in 1913 as a laboratory procedure to study the components of blood. No economist (or physician) then could possibly have extrapolated from that ancestral gadget to the "adoption" today of a descendent of that machine by a social security system, which did not exist at the time, at an estimated cost of \$1 billion a year by 1980. The machine can add 2 to 5 or more years of useful life to someone otherwise doomed to death in uremia.

Suppose that this ultimate use of dialysis had been predictable. Would the procreation of its primitive ancestor have been stopped? I will leave the moral aspects of the question with you. Could it have been stopped by law? Or by vigilante actions? I shall also leave that answer to you, for I do not have it, although I am willing to continue the search. Anticipation of development, and constraint, of technology on which a single useful life-of-quality may depend is excruciating business.

Of course, if Lewis Thomas were here, and if he has not wearied of his phrase, he might speak of the defects of half-way technology. An artificial kidney, a polio respirator and the like are expensive and enormously unsatisfactory. They play Jekyll to the Hyde of a "full scale technology", which is often relatively inexpensive, and either cures or prevents.

But half-way technologies offer some people meaningful life. There are 3 classes of experts who must be disqualified from the choice of rooting such partially successful interventions from medical care. They are physicians, politicians and the patients. Each class has too deep a reverence for or too great a stake in the value of a single life.

Some of the questions on half-way technologies and who pays the bills are splendidly summarized in Howard Hiatt's paper on the Medical "Commons".

His discussion makes clear that the real issue is not that of controlling costs by controlling research, but of developing acceptable, effective social mechanisms for controlling the ways in which the results of research are used. I not only agree, but accept the partial role of science in such development.

I hope that we, as a Nation, will be able to build a mechanism for establishing public consensus on these issues. It is not yet clear how this will be accomplished. What is clear is that if we can not afford to spend a billion dollars a year on dialysis those individuals who can not afford to pay for it themselves will continue to die.

What are the alternatives then? Research is a major hope. And this cuts across all of the determinants of health status. To say that major changes can only come from significant changes in life style does not eliminate

the need for research. What are the specific elements in our life style which produce health problems, and precisely through what mechanisms? These are research questions. What are the specific impacts of environment on health status and what can be done about them within the limits of the need to sustain a complex, urban, technology-based society? These too are research questions.

But research must be prudent. Its ultimate aim must be the cost-containing force of prevention. The eventual products of research must be anticipated, and where it is possible, a wise selection of alternatives to development made. Perhaps above all, science has an inescapable responsibility for validating those fruits it brings for distribution in the health care system.

Let me conclude with a few brief points about the costs of research and the returns which one can reasonably expect from it.

With so many demands on the public purse, how much should we spend on biomedical research, how cost effective is it. I don't know how much we ought to spend. I would say as much as we can afford. It has been said that any industry ought to plow at least 5% of its income back into research to assure its future. If this is any guide, we are well below that level now in relating supporting biomedical research to the increasing cost of health care.

How does one measure the cost effectiveness of research and for how long do we keep the books open. We don't have to worry about yellow fever any more, and we have closed that account. The methodology for assessing the cost effectiveness of research is not well developed, but available studies suggest that it is a gilt-edged investment. A recent study of the economic impact of surgical research concluded that in the single year of 1970, the United States had benefited to the extent of \$2.8 billion from a list of 16 surgical advances. The advances reduced death and disability from 20 disease conditions. The expenditure for the research which gave rise to those advances was but one-sixtieth of the benefit observed in the single year. The gains associated with the 20 conditions exceeded the entire national expenditure for all biomedical research in 1970. Since these gains not only continue but increase each year, it can be said that they alone "pay" in social terms for the entire national biomedical research effort each year.

Obviously, many research projects do not provide a rate of return at this level. But there is no doubt that the research enterprise as a whole is an excellent investment for the country. The savings which result from biomedical research are sometimes not visible, are easily forgotten, and do not produce annual royalties to support additional research. If significant improvements in health status are to be achieved, in terms of whatever determinant one chooses to emphasize, the benefits of good research will always outweigh its cost.

The Search For The Omphalos

The Oracle May Be In Your Own Hospital If You Work Hard To Retain The Authority

By Donald S. Fredrickson, M.D.

Recently I have been reminded that the stability of all things is relative. In late April, at a meeting of the National Academy of Sciences, Frank Press gave an illuminating lecture on the stability of the earth and presented a simulation of time-lapse photography of the changes in the earth's surface in a review of the now well-accepted theory of plate tectonics. In the film 500 million years of continental restlessness were collapsed into a little over three minutes.

DRIFT OF CONTINENTS

At the start, Africa and South America, bound as tightly as Siamese twins, emerged on a northward trek from the southern polar mass. As they migrated together North America sailed upward to the left separated from Africa-South America by the proto-Atlantic Ocean. Then this body of water disappeared as the three continents met in a whopping collision which produced among other artifacts, like crumpled fenders, the Appalachian Mountains. A single continent was formed called Pangea. It endured for a time only to break apart about 140 million years ago. (This explains the T-shirts adver-

tised in the Whole Earth Catalog emblazoned with the ambitious words "Reunite Pangea.")

The continental split formed the Atlantic Ocean. Africa drifted eastward pushing India into Asia to form the Himalayas; and Italy bumped into the underbelly of Europe with enough force to create the Alps.

The arrival of man, about a million years ago, was after most of the continental pushing and shoving had subsided. Each succeeding civilization found the earth relatively stable — immovable when compared with the day-to-day fickleness of the weather, the impulses of the gods, and the invasive tendencies of quarrelsome neighbors.

As Greece flowered in the sunny reaches of the Aegean, its gods with their characteristic hubris declared it to be the central zone of the earth. But where in Greece, the people asked, was the precise center? Zeus, perhaps because he had slept through geology lectures in the heavenly academy or perhaps because he was wise to the relative wink of time allotted mortals on the earth, agreed to fix the locus. He released two eagles, one from the east and one from the west, and caused them to fly toward each other. They met at Delphi. The place of their meeting was declared the center of the earth and marked by a stone in the temple known as the "Omphalos" (literally the navel).

DONALD S. FREDRICKSON, M.D., *Director of the National Institutes of Health, Bethesda, Maryland.*

Presented at the 50th Anniversary Meeting of The Miriam Hospital, May 3, 1976.

Editorial note: Also presented at the Birmingham Academy of Medicine, Birmingham, Ala., 5/10/76.

Not only was Delphi at the center of the Greek world, it was also the site of the Shrine of Apollo, where the gods could be called upon by mortals to solve their most perplexing problems. Thus Delphi became the source of the authoritative answer.

In the realms of science and medicine the center of the earth has shifted many times. As both professions have grown and civilizations have come and gone their centers of authority have subdivided and diffused.

Viewed historically the center of medicine has, down through time, wandered over the earth. Once it was considered to be located in the shade of a plane tree on the Island of Cos, where Hippocrates practiced.

Through the rise and fall of succeeding cultures it settled for a time in Renaissance Italy, then removed to the London of Sydenham, to the Leyden of Boerhaave, to the old Vienna School, to the Paris of Laennec, and back to the "new" Vienna school, whence the moderns in Germany and the United States drew their inspiration.

OMPHALOS IN COLORADO

When I was growing up the "Center of Medicine" took on a more specific if provincial meaning. I remember vaguely — and my mother has amply reinforced that recall — that when I was two or three years old our accessible center-of-the-medical-world was located in Pueblo, Colorado. Wasting away with a chronic sore throat, I was bundled up by my parents and hustled across the dusty plain in the old Chevrolet to the Pueblo Clinic where there was a bona fide pediatrician. He took one look at the bulging abscess beneath my tonsils. It was blue, for our well-meaning family doctor at home had liberally painted it with iodine. Hurriedly, he sent me on to the office of the clinic's nose and throat specialist. Why had Doctor Fritz Lassen wandered from Vienna to an ill-smelling western steel town, where his skillful lance was to be my deliverer from a premature death? I have often wondered as my debt to him annually compounds its interest.

Of course, our society has seen a vast improvement in the organization required for providing good, authoritative medical care since the twenties. One no longer feels impelled to go a thousand miles "to the Mayo's,"

the Delphic medical oracle of my childhood. Today, for you at home here, The Miriam Hospital and its partners in Providence will likely do as well as anywhere you could go.

Yet, with all the enormous advances in medicine as created by science, the search for the center of authority has not subsided. It has quickened in some quarters and has reached here and there a pitch of frantic urgency.

RISE OF NEW TECHNOLOGIES

The ability to intervene in man's endless struggle for adaptation and survival grows constantly. New technologies spring up everywhere from the rapidly spreading roots of knowledge. How they shall be used and whether they should or can be provided to all are questions which constantly create new problems. Whole continents of ethical, legal, and even economic concerns sometimes seem to loom on collision courses with medicine and science.

Ironically, though perhaps not surprisingly, some of our most difficult questions today result from the answers which have come from biomedical research in the years since The Miriam Hospital was opened 50 years ago.

Science has filled the doctor's bag and his anteroom with new tools to diagnose and treat, sometimes to cure, and best to prevent disease. These presents to society are sometimes wrapped in sticky problems and obligations.

QUESTIONS RAISED

The questions generated by the new medical technologies seem to be of three major kinds: 1) How far shall they be used to interfere with the traditional course of events? 2) How useful are they? 3) When they are useful, how do we see that all have equal access to them? (The authority that shall provide the answers to these three questions will not necessarily emerge from a single source.)

The first class of questions has become ever more urgent as we learn new means for drastic interference with natural processes, having the ability in some instances to stave off physical death for long periods of time but remaining unable to do more than just that.

The clinician's age-old question — "Can we successfully grapple with death in heroic ways?" — has been known of late to change its verb to "may we do so?"

Our imperfect state of knowledge has led to a few situations in which a totally conscious patient has become the long-time captive of a device required to sustain his life. You doubtless have read of the boy who for the past four years has lived his life in a totally isolated cubicle at NIH barred from direct contact with the outside world because his body has no resistance to infection. On the one hand a triumph of research and engineering. On the other hand, a poignant reminder of our failure. Why have we not yet found the way to less drastic treatment or, better still, to prevent such uncompromising disease.

A more familiar dilemma occurs when our technical ability exceeds the limits of philosophical wisdom. Such sometimes results from the development of mechanical means to sustain bodily functions. They restore countless useful lives, yet sometimes such equipment merely prolongs life for protracted periods in the absence of brain function. Many physicians and many families have been tortured by the consequences of this partially successful interference with natural process. It has started searches for a new definition of death. Here the answer cannot come from the temple of science. Lacking an oracle, the clinician and family must find a broader consensus, as in the courts and legislative bodies, to help them distinguish life from death. A convenient, simple authority is not available. The whole of society must become its own authority on such things.

COST OF LIFE

Questions of the second kind about technology are usually less dramatic, but involve the welfare of far larger numbers of people. They are concerned with the issue of whether some test, drug, or other intervention is useful and safe.

(The same humanitarian and noble purpose that has prompted the development of highly successful means for prevention, cure, or treatment of disease can sometimes be responsible for introduction into widespread use of interventions which at first appear

to be helpful, but later may be found to be of no help or even injurious.)

How many of you have read Michener's recent novel *Centennial*? Do you remember the tragic story of the farmers in northeastern Colorado? How they were persuaded that new methods of cultivation would produce large crops of wheat on the high plains drylands? Even though the rainfall was far below the amount generally considered to be necessary. The secret was to catch, store, and protect from evaporation whatever rain fell on the land. But this involved plowing deep furrows and discing and harrowing to make a smooth surface of finely divided topsoil. The idea was widely adopted and for 20 years was highly successful. The few naysayers were brushed aside with the crop reports which gave the lie to their doubts. Suddenly, in about 1920, the fatal flaw became apparent and came close to destroying a large portion of the west. For the pulverized soil on the vast denuded areas was easy prey to the dry winds which periodically swept down from the mountains. Because the weather and wind cycles are measured in tens of years, and the plains previously had been protected by the sod, the tremendous dust storms of the early thirties were unprecedented.

The nightmare situation which Michener described so eloquently was created by well-intentioned and apparently intelligent innovation. It is a chilling reminder to the researcher and the clinician that similar flaws may be hidden in new and promising means of therapy. The caution engendered by such considerations must be balanced against the understandable impatience of the public and its representatives who wish to see the "latest and best" employed against the enemies, disease and disability. One of the most necessary and most difficult phases of biomedical research involves the demonstration through the conduct of clinical trials that an intervention in man is safe, practical, and efficacious. Clinical investigation is tough.

It is also expensive.

CLINICAL TRIALS

The NIH is now conducting some 1,000 clinical trials and is investing more than 10 per cent of its research budget in this ac-

tivity. Some of these trials are large. Thirty-one involve more than a thousand subjects chosen on a randomized basis.

We believe that such studies are important. They often are the only means for testing and evaluating new hypotheses. They can prevent premature introduction of interventions into practice.

The outcome of clinical trials in the future will likely determine the patterns of practice, which will, in turn, set the terms of reimbursement and standards of quality care.

Long-standing and traditional modes of therapy are a particularly troublesome class of problems to put to clinical trial, and yet the answers from such trials may be equally as important as the results from trials of completely new technology. This week a Senate committee is holding hearings on why there are still such differences of opinion regarding the treatment of breast cancer, a difficult issue to settle in a hearing room, but it shows the width of the gap between public expectations and our power to resolve certain critical questions, or to explain to public satisfaction why the answer is so elusive.

There is a tendency in these times to conduct the search for the medical Omphalos in the neighborhood of Washington, D.C. A few would locate it in Bethesda, where the NIH has its campus and hospital. Others would cart it away to the mall, where it might be within walking distance of both Executive Offices and Capitol Hill. And within reach of on-line cables to the Government Printing Office, for a central authority in a land of 200 millions means much communications traffic between the concerned and the source of assurance.

Despite the continuing sounds of construction, it is not likely that a functional oracle will be added to the things to be visited in Washington when the blossoms are out in the nation's capital. The tradition of the land is pluralistic and resistant to excessive central control. There is a great dispersion of the search for knowledge and its practical application, and sources of authority are nearly always in geographical proximity to all.

AUTHORITATIVE DIRECTIONS SOUGHT

But it will be foolish if we pay no attention to the principal urge for more authoritative directions in matters of health.

It is the cost of health care. In the United States in 1940 less than 5 per cent of the gross national product was spent for health. Now it is 8.5 per cent, and soon it will be 10. A figure of \$118 billion is estimated for the present year, and the upward deflection of the curve is greater than the general inflation. For General Motors the medical package per worker is said now to be about \$1,800 per year. The federal purse, which now buys more health care than any other, is suffering strain.

Because no one may argue with an equally pressing mandate to make the same standard of care available to all, this theme is added to a general one of cost containment. The solution we must seek is to make equal access available to what is necessary and proved to be effective with efficiency in delivery.

There are flaws in our current system. In deciding what innovations are effective enough to replace older modes the informal collegial ways of coming to decisions are not maximally workable for the times. The great network of academic medical centers and developers of technology have to find some ways to improve the process — to couple it with statistics and economics when possible, making evaluations called for by the times.

VOLUNTARY SYSTEM MUST RESPOND

The voluntary system, which has served the country well, must also respond to new and increasing demands. Where excellence is unevenly available, where costs are forced upward by hospital practices or a lack of community organization, collective authority has to be mobilized at local and regional levels. It must function well, or central authority will be created, like it or not.

At the center of the storm over the costs of health is a problem of particular interest to us all: It is the question of whether cost accounting must consider only populations, with the submergence of persons. The artificial kidney is a case in point. Some urge that we stop the development of new means

to help a few at considerable cost to the many. If this is even possible, we shall have to find other authorities than physicians, patients, or politicians whose concern with single lives is too tight to allow them to be objective.

Who will be the oracle for these decisions? Where will be the Omphalos? For some things it will be in one place, for others it

will be elsewhere. In some critical things that matter the most to you about your health, it will be up to you, your physicians, this hospital you have built, this community to work hard to retain this authority here.

National Institutes of Health
9000 Wisconsin Avenue
Bethesda, MD 20014



REMARKS

by

Donald S. Fredrickson, M.D.
Director, National Institutes of Health

at

Wall Hanging Dedication Ceremony
Perinatal Clinic
Clinical Center
May 6, 1976

It was made very clear to me that my function at this presentation is solely to provide greetings and introductions. Afterwards, I, along with the other men present, have been told to stand here and be decorative. This is a lovely moment during the two-week "Women in Science" Celebration we are having, and I am pleased to be present when we dedicate this gift, a beautiful batik wall hanging, from the women of NIH to the Pediatric Service of the National Institute of Child Health and Human Development.

More and more women are part of the work force today. Over 15,000,000 women are working. Not only for economic reasons, but also for personal fulfillment and because their talents and skills are needed. Many of these women have had and are having babies while continuing to provide indispensable resources for the work force.

If for no other reason than to guarantee that these resources are continually available, the NIH is firmly committed to equal rights and opportunities for women--both those who work here and for those everywhere. One of the most significant ways we can show our total commitment is through the research and clinical work of the Institute most directly concerned with mother and children, the NICHD. We have always understood that the good

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health of our nation's children is fundamental to the good health of the whole population. But we must also realize the social and economic benefits derived from having healthy mothers and mothers-to-be. Many women work right through pregnancy and return to their careers soon after their babies are born. And we know that a healthy pregnancy, a healthy baby and a strong mother all make this possible. This serves to underscore the importance of motherhood while at the same time recognizing the expanding role of women and the progressive role all parents play in the welfare of their children. For all these reasons, this Institute and this service have been selected for this gift presentation during our "Women in Science" Celebration.

It gives me great pleasure first to introduce the artist who created this beautiful wall-hanging, Jill Lindau. I understand this is her son, Jay, with her.

Presenting the wall-hanging for the women of NIH is Mrs. Annie Collins of NHLI, who, along with being a long-time and greatly respected member of the NIH community, originally suggested this as a part of "Women in Science," and Ms. Aggie Sweeney, who works in the Office of the Assistant to the Director, NICHD, and is also a member of the NICHD Women's Committee, the first of many, I hope, at NIH.

Receiving the gift on behalf of the Pediatric Service is Dr. Sharon Levine and Nurse Sharon Wofsy.

(Pose for Photographs)

COMMENTS ON PRESENTATION BY G. W. THORN:*
METABOLISM AND ENDOCRINOLOGY

by

Donald S. Fredrickson, M.D.**

I have enjoyed Dr. Thorn's thorough and interesting review. Certainly if one includes under metabolism the adaptation of biochemical knowledge to the reduction of disease to molecular terms, no other field has developed to a more astonishing degree in the last 50 years.

I would also emphasize, as he has done, the British and European roots that nourished the splendid flowering of new knowledge in endocrinology and metabolism which occurred in North America after about 1920, especially after 1945. This is true not only for insightful hypotheses--such as those transmitted from the Old World by the "Great Men of Guys," or Claude Bernard, Archibald Garrod, and others.

It is also true for many of the new techniques and methods that opened the doors to so much discovery.

It is not yet clear to all who participate in setting priorities for research, that the strongest hand in its direction is that of Technical Opportunity. The mating of method with a new generic chemical compound of great biological significance--like the cyclic nucleotides or prostaglandins--or a novel biological process--like hypothalamic-releasing hormones or cell membrane receptors--can quickly spawn several generations of rewarding research. Research that is applied in every literal sense, yet often is no

*Remarks at the Colloquium on the Bicentennial of Medicine in the United States, May 7, 1976, Masur Auditorium, National Institutes of Health

**Director, National Institutes of Health, Bethesda, Maryland

less fundamental and essential if basic principles are to be adapted to improve the human condition.

In a research career that began in 1950 and only quite recently has vaporized into practical philosophy, I have had a marvelous and practical exposure to the timid entry and dazzling growth of much of the method that has been so critical for growth of biological knowledge in this period.

Radioactivity

The history is long and sometimes sobering from Democritus through Dalton, Rutherford, Bohr to the Bomb. The beneficial fallout in isotope technology, however, was the cornerstone of metabolic research in the 50's.

The more energetic isotopes of I, K, and Cr were manageable with Geiger-Muller tubes, but the soft betas of the key atoms in biochemistry at first required the cumbersome plating of Ba CO₃ or proportioned counting of methane. It was a time when I. L. Chaikoff in Berkeley could parley a couple of radionuclide chemists and a vast stable of eager postdoctorals into a brief, but pace-setting monopoly of the JBC. The first hits were inevitably the catabolic cycles, but it was not long before anything synthesized from labeled H₂O, CO₂ or acetate came to have its biochemical ontogeny charted on the laboratory walls.

(First test of commercial liquid scintillation counting done here in the Clinical Center by Peterson and me.)

Chromatography

Isotopic measurements, however, were usually dependent on specific activity. Few of the new wave of endocrinologists and metabolists had the

skills or patience of organic chemistry and found it much more desirable to leave the process of purification to a roll of paper in a jar full of vapor.

American science here has much to thank colleagues abroad. From the Russian Tswett, who separated colorful carotenes on crude columns, through the Swiss and Germans came a succession of new ways of lazy separations that found here ingenious and extensive adaptation to biological experiments. Perhaps the most native contribution in this area was the use of ion-exchange resins.

To the British we are enormously indebted for gas chromatography. What British industry found uninteresting, we developed to extraordinary advantage. It took the Swede, Ryhagen, at the Karolinska to tie up the mass spectrometer to g.l.e. to bring it to the apex of nanomolar discrimination.

Cell Fractionation

Because it had a near monopoly on ultracentrifugation, the separation of cellular organelles became an important American contribution. To a real extent, the aesthetic qualities of such fine dissection were not realized until the electron microscope arrived. To see a mitochondrion is to believe in one.

For medicine, the JRS and the Golgi have not yet had the glorification that has come to the lysosome. Conceived by DeDuve, a Belgian who finds it congenial to work much of his time in New York, the lysosome has recently shared one of molecular medicine's finest hours. This is the swift dispersal of a clot of eponymic diseases into specific deficiencies of lysosomal

hydrolases. I cannot restrain an element of local pride to mention the singular contributions of NIH's Roscoe Brady in the area of sphingolipidoses and Elizabeth Neufeld in the mucopolysaccharidoses. Their combined score is near to ten disorders, laid neat and clean, plus the beginning of a basis for rational therapy for some.

Of course, this has been just a slice of the remarkable development of power to resolve metabolic questions that has brought this bicentennial period to a close. Its dazzling acceleration has important consequences:

1. The growing power of science has forced introspection as to its uses. This is not detrimental. Even we who think we understand it all may have failed to comprehend some implications.
2. There is no perceivable limit to the ultimate penetration of the processes of life. As the complexities of understanding increase, they force a paradox; the knowledge can neither be gained nor guarded by one class of citizens alone. The enterprise becomes increasingly collective.

To convey the meaning of it all to diverse patrons, and thereby to gain support to continue, places an ever-increasing burden on the medicine and science of the last quarter of this century. I do not think we should despair that we will not be able to bear that burden.

THE SEARCH FOR THE OMPHALOS*

Donald S. Fredrickson, M.D.**

An article of NIH faith, confirmed by experience, postulates that our principal strength is drawn from the members of the nation's scientific community who serve as our advisors. And Birmingham is the home of an unusually large number of our consultants.

Seven of our 12 national Councils or Boards have members who live here. The University of Alabama, Birmingham, is among the top ten out of 260 institutions in terms of the numbers of its scientists who serve on grant-review committees or councils.

Our current committee roster includes 35 from UAB, four from Southern Research Institute and one from Miles College.

If it were not for the conflict of interest statutes I might try to set up a Birmingham to Bethesda airline.

Our heavy draft of your talent is a reflection of the high regard in which your scientists and institutions are held - concrete evidence of the pervasive and continuing influence of giants like Tinsley Harrison and Champ Lyons and a sincere accolade to imaginative and energetic leaders like Joe Volker.

* Presented at the Birmingham Academy of Medicine, Birmingham, Alabama on May 10, 1976.

** Director, National Institutes of Health

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But the men I have mentioned and the many others who ought to be named would be the first to warn that excellence is not a steady state phenomenon.

Recently I have been reminded that the stability of all things is relative. In late April, at a meeting of the National Academy of Sciences, Frank Press gave an illuminating lecture on the stability of the earth and presented a simulation of time-lapse photography of the changes in the earth's surface in a review of the now well-accepted theory of plate tectonics. In the film 500 million years of continental restlessness were collapsed into a little over three minutes.

At the start, Africa and South America, bound as tightly as Siamese twins, emerged on a northward trek from the southern polar mass. As they migrated together North America sailed upward to the left separated from Africa-South America by the proto-Atlantic Ocean. Then this body of water disappeared as the three continents met in a whopping collision which produced among other artifacts, like crumpled fenders, the Appalachian Mountains. A single continent was formed called Pangea. It endured for a time only to break apart about 140 million years ago. (This explains the T-shirts advertised in the Whole Earth Catalog emblazoned with the ambitious words "Reunite Pangea.")

The continental split formed the Atlantic Ocean. Africa drifted eastward pushing India into Asia to form the Himalayas; and Italy bumped into the underbelly of Europe - with enough force to create the Alps.

The arrival of man, about a million years ago, was after most of the continental pushing and shoving had subsided. Each succeeding civilization found the earth relatively stable - immovable when compared with the day-to-day fickleness of the weather, the impulses of the gods and invasive tendencies of quarrelsome neighbors.

As Greece flowered in the sunny reaches of the Aegean, its gods with their characteristic hubris declared it to be the central zone of the earth. But where, in Greece, the people asked, was the precise center? Zeus, perhaps because he had slept through geology lectures in the heavenly academy or perhaps because he was wise to the relative wink of time allotted mortals on the earth, agreed to fix the locus. He released two eagles - one from the east and one from the west and caused them to fly toward each other. They met at Delphi. The place of their meeting was declared the center of the earth, and marked by a stone in the temple known as the "Omphalos" (literally the navel).

Not only was Delphi at the center of the Greek world, it was also the site of the Shrine of Apollo - where the gods

could be called upon by mortals to solve their most perplexing problems. Thus Delphi became the source of the authoritative answer.

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Of course, our society has seen a vast improvement in the organization required for providing good, authoritative medical care since the twenties. One no longer feels impelled to go a thousand miles "to the Mayo's" - the Delphic medical oracle of my childhood. Today, the range of professional expertise and medical care facilities available to residents of the Birmingham area is on a par with the best that can be found anywhere.

Yet with all the enormous advances in medicine, as created by science, the search for the center of authority has not subsided. It has quickened in some quarters and has reached here and there a pitch of frantic urgency.

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It is also expensive.

The NIH is now conducting some 1,000 clinical trials and is investing more than 10 percent of its research budget in this activity. Some of these trials are large. Thirty-one involve more than a thousand subjects chosen on a randomized basis. The University of Alabama, Birmingham, is participating in 13 of our larger trials.

We feel such studies to be important. They often are the only means for testing and evaluating new hypotheses. They can prevent premature introduction of interventions into practice.

The outcome of clinical trials in the future will likely determine the patterns of practice, which will, in turn, set the terms of reimbursement and standards of quality care.

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When he invited me to participate in this meeting of the Academy, Dr. Hazelrig asked me to discuss the impact of the Federal government on the practice of medicine. In a sense I have addressed the complement of that issue.

There is a tendency in these times to conduct the search for the medical Omphalos in the neighborhood of Washington, D.C. A few would locate it in Bethesda, where the NIH has its campus and hospital. Others would cart it away to the mall, where it might be within walking distance of both Executive Offices and Capitol Hill. And within reach of on-line cables to the Government Printing Office, for a central authority in a land of 200 millions means much communications traffic between the concerned and the source of assurance.

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The Medical Information Service by Telephone (MIST) which you have developed here is highly effective in enhancing that proximity. We have mentioned the MIST system several times in our Congressional testimony as an example of the successful application of a practical idea. The same creativity that has made MIST a reality is evidenced in your Health Extension Learning Program involving Agricultural Extension workers. The only reservation I feel about them is that with the names MIST and HELP you threaten that great acronym factory on the Potomac.

But it will be foolish if the nation as a whole pays no attention to the principal urge for more authoritative directions in matters of health.

A prime issue is the cost of health care. In the United States in 1940, less than five percent of the gross national product was spent for health. Now it is 8.5 percent and soon it

will be 10. A figure of \$118 billions is estimated for the present year, and the upward deflection of the curve is greater than the general inflation. For General Motors the medical package per worker is said now to be about \$1800 per year.

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The voluntary system, which has served the country well, must also respond to new and increasing demands. Where excellence is unevenly available, where costs are forced

upward by hospital practices or a lack of community organization, collective authority has to be mobilized at local and regional levels. It must function well, or central authority will be created, like it or not.

At the center of the storm over the costs of health is a problem of particular interest to us all. It is the question of whether cost accounting must consider only populations, with the submergence of persons. The artificial kidney is a case in point. Some urge that we stop the development of new means to help a few at considerable cost to the many. If this is even possible, we shall have to find other authorities than physicians, patients, or politicians whose concern with single lives is too tight to allow them to be objective.

Who will be the oracle for these decisions? Where will be the Omphalos? For some things it will be in one place, for others it will be elsewhere. In some critical things that matter the most to you about your health, it will be up to you - your physicians, the facilities you have built, this community - to work hard to retain this authority here.

I mentioned at the beginning of my remarks the prominent place Birmingham now occupies in the national biomedical panorama.

I would be remiss if I should fail to acknowledge the debt owed by the entire research and medical care community to Senator Lister Hill. We were honored by his presence at a dinner in Bethesda last Thursday. His advocacy and unstinting support of excellence in research and medical care broadened our horizons of hope today and challenge us to continue the adventurous search.

OPENING REMARKS*

by

Donald S. Fredrickson, M.D.

I am happy to join you at this Awards Assembly and to extend my warm congratulations and best wishes to all those who are receiving degrees and honors today.

To those of you who are visiting NIH for the first time today, to the families and friends of the graduates and award winners, I want to welcome you to our campus.

I use the word "campus" advisedly, and in a double sense. Because of the atmosphere and spirit of learning which is our purpose, this facility has long been familiarly known as a campus; and, of course, it is a campus house of the Upward Mobility College of the Federal City College. We know that FCC uses other government locations for its upward mobility courses, but there is none more suitable than ours, with grassy lawns and tree-shaded walks, an ivy-covered wall here and there, even our own share of absent-minded professors (some of them in white coats). About all we lack is the cheerleaders (from where I sit it sometimes seems that the Bronx cheers outnumber the other kind).

I have been talking essentially about the physical surroundings which, although pleasant enough, are really superficial. We resemble a campus in more substantial ways. This is a center of learning and discovery. Our people have restless, probing, inquiring minds. That is what research is all about.

*Presented at the Upward Mobility Awards Assembly, June 4, 1976
NIH, Bethesda, Maryland

It is also what a college is all about. It is where the quest for knowledge and the desire for self-improvement come together. It is entirely natural and logical that NIH should be the home of an Upward Mobility College. Our commitment to upward mobility grows out of our dedication both to learning and to the advancement of the human condition.

The students we are honoring today have shown a similar kind of dedication. Their initiative in enrolling in a college program, their willingness to work hard, their determination to succeed against sometimes sizable obstacles, are worthy of our highest praise. Their experience has added immeasurably to their sense of self-confidence and self-worth. Their career horizons, once perhaps quite limited, are now considerably broadened.

I salute all of them who have taken that extra step to realize their full potential, to pledge that what they set out to do they will do as well as they can. Speaking for all of NIH, I am proud of what they have already accomplished and for what this accomplishment means for their own future and for that of their families, friends, and community.

On behalf of the entire NIH family, let me say how much you honor us today with your accomplishments. You have our sincere wishes for the future and our promise to do what we can further here to bring ever greater measures of success and fulfillment in your lives as part of this Institution.

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The government role in biomedical research

DONALD S. FREDRICKSON

National Institutes of Health, Bethesda, Maryland 20014

This symposium has been constructed as a musical canon. In each of our performances you will hear similar themes, running in different key or sequence.

I am to consider the role of government in biomedical research. I will attack my theme forward and then retrograde, for the role of biomedical research in government is the other important side of an easily reversible and now inseparable relationship. Some form of accommodation of science by the state is as old as science. It is a source of tensions that wax and wane. It changes often and has been much discussed.

A new state of transition now dominates the relationship between government and biomedical science. It is similar to one that occurred earlier in nuclear physics. In my view it is of profound importance that we see this transition in correct historical perspective and grasp its significance, for the passage through these straits is delicate and there is much at stake.

I will restrict my analysis to the National Institutes of Health—as an institution and as a constituency. Because of the dominant role of the NIH in underwriting and self-engagement in biochemistry, in particular, and biomedical research in general, the example is not a trivial one.

The NIH is an almost unique example of government patronage and power to influence science. For nearly 35 years it has been the means of permitting extraordinary self-governance by a profession in the distribution of public resources to itself—yet with fully accountable public administration and continuing congressional oversight. Over this period the NIH has been the center of the enormous growth of biomedical science, in this country and in the rest of the world. I refer to the whole enterprise, of course, and not only to the home campus of the NIH—although the number of papers it produces annually is exceeded only by

one other institution: all of the University of California campuses combined. The NIH also supplies half of all the federal funds that form a substantial underpinning for the nation's academic medical centers.

You are aware that a Presidential Panel has recently completed an extensive reexamination of the NIH and of its sister agency, the Alcohol, Drug Abuse, and Mental Health Administration, which is responsible for mental health, alcohol and drug research. This study had a different mandate and resulted from a different mood about biomedical research than the last such national study conducted in 1965 by the Wooldridge Commission. In 1965 the NIH was in a period of exuberant growth and the only question was whether a budget then rising well above one billion dollars a year was being spent wisely and with full fiscal accountability.

With the late 1960's, there began a significant change in relations be-

tween government and biomedical science. The dramatic rise in purchasing power for the enterprise as a whole started to level off. The exception was the surge of resources channeled into study of neoplasia, a move accompanied by political actions and emphasis on more directed objectives. The leadership of the NIH was destabilized and the flame seemed to flicker as congressional oversight and executive actions changed force and direction. In 1973 the Agency ceased to be the bursar for federal capitulation for education in academic medical centers. The rising tide of costs set in motion waves for reform of the health care system that also buffet biomedical science and the institutions in which it has thrived.

The present era has several distinctive characteristics. Some have been repeatedly emphasized. Among them are:

- the increasing competition for federal resources and self-imposed limits on congressional appropriation ceilings.
- a marked restriction, for the present at least, in *growth* of purchasing power for science.
- a countervailing increase in expectation and demand that science tend to urgent practical problems.

What really marks the new era, however, is less these three than another factor, and that factor is: the ascending power of science. From the gentler years of exploration, there now flows from biology an increasing current of new technology. Natural selection has disappeared, and in its place have come the control of fertility; means for determination of fetal fitness as well as for abnormal extension of life; surrogate organs; possibilities of genetic recombination; and the prospect of changing the limits of adaptation.

Others on this symposium will expand upon other aspects of these promises and problems. I am concerned here with what such issues mean in more political terms. The inevitable consequences are:

- an interdependence of government and science not heretofore experienced. To the simpler rules of fiscal accounting have

been added the more complex calculus of costs and benefits.

- an intimate involvement of science with administrative laws and regulations, enmeshment in an intersecting net of concerns for morality, ethics, effects on the environment, the economy, and other changing social imperatives.

It needs to be said. Having come into an inheritance of social responsibilities it did not anticipate, the old NIH is gone. Its unparalleled growth, the relative privacy of its enterprise, and its solitary role in the federal support of the academic medical centers have become subjects for nostalgia. To the extent that this is true for the NIH, so is it true for biomedical science in general.

In these last few years, some have spoken of the NIH and biomedical research as having seen the passing of the Periclean Age. Whether true or not, the analogy is worth pursuing, for in the decline of the Athenian city—state there is a lesson for science.

Toynbee's massive analyses of history are not my favorite reading; nevertheless he has said some interesting things about the disintegration of Hellenic Society. In his opinion, the Athenian failure was one of lost initiative. It could not and would not bring off federation with the expanding civilization it had spawned. Parochial in its sovereignty, the elite and creative city both disdained and failed to understand the political and economic dictates of a changing civilization.

It is the nemesis of creativity, Toynbee implies, to idolize its own institution to the point of missing voluntary accommodation to changing realities. Thus, the isolation of Athens in its golden age was doomed to be ended, but its creative brilliance need not have lost its lease on survival.

So it is true of the NIH and of science emerging from a more parochial period. The surviving elements are a vigorous community of science with a proud record of achievement and unlimited promise. The internal ethic of biomedical science is strong and has proved it can participate in a remarkably effective and honest way in the allocation of its own resources. Inherently

conservative, it has nevertheless remained creative. While passionately reductionist in approach, biological science has remained basically humanistic. The American community is presently the leader, but it is only one part of a worldwide community with the same characteristics.

What, then, is now the role of the NIH—or more generally of the federal government—in a period necessitating greater enlightenment and cooperation between government and science?

It is: 1) to maintain the capacity and effectiveness of the apparatus now constructed for scientific inquiry; and 2) to foster the public interest in wise utilization of knowledge for human betterment.

These are not superficial requirements. They are highly complex at their base. I hope that the executive branch and the Congress will come to abandon certain adversarial roles of differences that have destabilized American biomedical research. The height and sincerity of political interest in research is heartening, however, and people in positions like mine feel a compelling responsibility to help laymen in government:

- to understand the organic nature, and the perishability of the human and physical capital now invested in science.
- to be cautious that the productivity of research not be stifled by inflexible regulation or rigid mandates for discovery that are responses to political pressure rather than scientific reality.
- to continue to believe in the self-governance of the system by the participants as assuring its maximum efficiency and effectiveness, and
- to exact wisely from these participants and from that system the full measure of responsibility to the public interest.

In all these things the NIH and the National Science Foundation as curators of public trust—and the NIH as a principal research arm itself—have roles that transcend their older, more traditional ones.

We have to understand better the anatomy of the research organization and its life processes and to defend some arbitrary level of ac-

tivity as a minimum investment for the nation. We have to maintain wisdom in rational distribution of that investment—in different forms of support—in training of new entrants into specified fields, and to insist on integration of efforts to stabilize the universities and institutions in which the search continues.

It is not enough, however, to understand thoroughly the process of research or that biological knowledge is currency convertible to the public good. There are needs in health that cannot be met by research, or have not been met by research, or may even be created by research. And we have to understand these, too, and pay a tithe toward their solution.

The community of science cannot escape its responsibilities when useless objects have entered or been kept in the doctor's bag through lapse of interest in practical development or because our system for creating authority on benefit and effectiveness is too casual or informal.

The really diagnostic symptoms of the new era, however, are the cries of fear of the consequences of some new laboratory achievement.

Many of you will have already read a letter in the June 4 issue of *Science*, written by a senior member of the American Society of Biological Chemists "On the dangers of genetic meddling." In it I read the abandonment of belief by a scientist in the capabilities of his profession to engage as a partner with government in the promulgation of codes for experimentation designed for the protection and benefit of the public.

If he is right, then science is doomed. And so, by default, is mankind, if continued enlightenment and knowledge, and the prudent advice of the most informed, count for survival.

Such a dismal view will not prevail, but we may be grateful at least for the reiteration of challenge and reminder of responsibility.

The NIH, a part of science within government and a piece of govern-

ment within science, is in the midst of the growing concern in such matters. The interests of the public and of science can be served jointly, and we will be among the leading institutions to find how this can best be done.

Public participation . . . societal choice. This is only one aspect of an interesting agenda. As each polynomial—"technology assessment," "environmental impact," "informed consent"—is reduced to the roots, we learn to cope. For example, it will not be news to you that the differences in quality of closely related research proposals cannot be settled by general referendum in town hall. But it is also true that open, candid debate with the public on genetic research or technological priorities in NIH conference rooms has not resulted, either, in Jacobin anarchy or Girondist terror. There is a middle way through these turbulent and interesting times. Let us keep our confidence and attend wisely to the affirmatives.

Ep

MEETING OF THE
ADVISORY COMMITTEE TO THE DIRECTOR, NIH

JUNE 10-11, 1976

OPENING REMARKS BY DR. DONALD S. FREDRICKSON, DIRECTOR, NIH

Good morning, Ladies and Gentlemen. It is a great pleasure to welcome the members of the Advisory Committee to the Director of NIH. This is a fluid organization. Each time it seems to be almost a new one. The Committee was initiated in 1966 and by 1975 had, for one reason or another, dwindled down to five members. As of the beginning of this year, we have persuaded four of those five members whose terms of service would have ended at the end of this month to continue for another year. These members are: Jim Kelly, who is the Executive Vice Chancellor for the State University of New York; Bob Petersdorf, who is Chairman of the Department of Medicine at the University of Washington School of Medicine; Joseph Dodds, who is Medical Director in the Campbell General Hospital at Chattanooga; and Charles Sprague, who is the President of the Health Science Center at the University of Texas. Both Drs. Dodds and Sprague are unable to be here. One other member of the holdover group who is also unable to be here is Roy Hudson, President of the Hampton Institute in Hampton, Virginia. I am very grateful to all of you who have agreed to serve one more year on this Committee.

I am very pleased, now, to be able to introduce some new members sitting with this Committee for the first time. Let me introduce them to you as best I can: Dr. Julius Comroe, a long-time friend who has been a member of a number of NIH committees, and is the Emeritus Director, of

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the Cardiovascular Research Center in San Francisco; Dr. James Gustafson, who is Professor of Theological Ethics at the University of Chicago; Mr. Jule Hannaford, an attorney from Minneapolis; Ms. Rebecca Martinez, who is a medical student at the University of New Mexico; Dr. James Neel, Professor of Human Genetics at the University of Michigan Medical School; Dr. Katharine Sturgis, Emeritus Professor in the Department of Community and Preventive Medicine at the Medical College of Pennsylvania; Dr. Sidney Udenfriend, indeed an old NIH-er, who left some years ago from the National Heart and Lung Institute to be Director of the Roche Institute of Molecular Biology in New Jersey; Dr. Victoria Stevens, who was a medical student and now is a graduate of the University of Arizona; and Dr. Jeanne Sinkford, Dean of the College of Dentistry, Howard University, a new member who is unable to be with us today--she has the flu! One other new member is unable to be present; that is Dr. Hans Muller-Eberhard, Chairman of the Scripps Clinic and Research Foundation in La Jolla, who had to be in Europe and was very sorry not to be able to come today. I am very pleased to welcome all of you, as well as the ones who cannot be with us today, to service on this Committee.

We will also be privileged to have with us a number of special consultants today, they include; Dr. David Hamburg, the new President of the Institute of Medicine, who is most welcome; Dr. Edmund Pellegrino, Chairman of the Institute of Medicine Advisory Committee on Social Ethics in Health; Dr. John Jennings of the Food and Drug Administration;

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Dr. James Childress, who is Joseph P. Kennedy Professor of Christian Ethics at the Kennedy Institute in Georgetown. Others will be introduced when they arrive. Several representatives from the HEW Commission for the Protection of Human Subjects will be with us later. Drs. Aller, Caplan, Menkes, and Rabin from the National Science Foundation will also be attending today's session. Tomorrow afternoon we will have, also, a representative from the National Bureau of Standards and several consultants representing the Office of Technology Assessment.

I would like to settle one or two mundane matters, but necessary ones. First, if possible, we would like to set our calendars for the next year. Let me give you two dates that we would like to meet, then we will at a later time collect your anxieties or problems with those. They are suggested to be November 4-5 of 1976 and March 3-4 of 1977. I think we will wait until perhaps the break at noon and you might tell us then whether these are acceptable or not.

The Deputy Director of NIH is going to have a briefing for new members at 8:00 a.m. tomorrow morning. This is an optional part of the program that has been particularly arranged for those who are quite new to the NIH, but those of you who are experienced NIH-ers might find it very useful to have an updating on its mission and the way it goes about its business.

As we proceed into a day in which the mythical evaporation of the Potomac may indeed occur, we have here within this room a fairly difficult

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and also warming agenda. Part of the inheritance of the new NIH--in this a transitional era in which biomedical science and NIH find themselves--is an inheritance of new social responsibilities. This meeting is going to be devoted to a consideration of one of these--the question of the appropriate role of NIH as a piece of government in science and part of science in government; the role of this organization in the assessment of the impact of biomedical technology. It is clear that many of the improvements in the quality of modern life are a direct result of scientific research and technological development but it is increasingly apparent that some of the new technology is a mixed blessing. I think the recognition of the increasing frequency of unanticipated consequences of technology stimulated a great deal of concern about earlier evaluations of the potential impact of new and expanding developments from research. Attention to the social impact of biomedical technology is relatively recent as compared with the attention engendered, for example, nearly twenty years ago by nuclear physics. I think that biomedical science, in a way, has now come to the same stage of relationship between the state and science that now exists, and has existed in the past two decades for nuclear physics.

We now find that the power of biomedical science is ascending rapidly. Natural selection has disappeared and we are now able to determine the sex and the fitness of the fetus in utero. We have the ability to replace organs to maintain functions of the body, extend life, perhaps even to change the limits of adaptation, and we have extraordinary new opportunities

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and challenges in the field of genetic recombination, for example. And all of these things have focused increased public attention and public controversy upon the implications of biomedical science and technology.

In 1966 when Mr. Daddario, who will be here later today, was a member of Congress, and Chairman of the House Subcommittee on Science Research and Development, there was coined the term "technology assessment." It was meant to describe the policy analysis that attempts to provide a balanced appraisal of the potential benefits as well as the undesirable consequences of emerging technology. Mr. Coates of the later established Office of Technology Assessment, has described technology assessment as "a special class of policy studies which systematically examine the effects on science that may occur when a technology is introduced, extended, or modified with a special emphasis on those consequences that are unintended, indirect and delayed." Note the emphasis placed on the assessment of the secondary and the higher order consequences of technology rather than on the technology itself. Technology assessment goes beyond consideration of the effectiveness of a new technology in achieving its intended purpose. The attempt is to evaluate the economic, the ethical, the legal, and the broad societal implications that the introduction of that technology portends.

It is the policy analysis of unintended, indirect, and delayed social impact that should serve a useful purpose in focusing our discussion here today and tomorrow morning. I think we will exclude from consideration

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those activities such as controlled clinical trials, which are undertaken to determine the primary efficacy and safety of a new medical regime or device. They are indeed a part of technology assessment, but we are going to attempt to deal with other matters that, in one sense, are more difficult or even more abstract. You have in your books a letter that Senator Jacob Javits wrote to us and he notes that the clinical trials are an important instrument. The NIH is supporting now about 800 trials, depending on how you define them, on a broad spectrum of disease areas. There are a number of important policy questions about these, particularly in connection with NIH support for clinical trials. We have a Clinical Trials Committee working on these questions and it will be useful to have, at another meeting of this group, a report and an examination of what that committee is seeking to do in assisting the B/I/D's of the NIH to go about the business of conducting an examination of specific questions on clinical application of research. Clinical trials, however, don't directly assess the broad concerns that are inherent in technology assessment. As Senator Javits suggests, we must go beyond the question of efficacy to examine the broader social questions in technology development. And for the same reasons then, demonstration projects which are designed to determine the effectiveness of new disease control technology in community based settings will be emphasized in our analysis during this meeting.

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The agenda for today's meeting is structured to provide a brief background of the NIH concern with technologies that are in different stages of development. Dr. Benjamin Burton, Associate Director for Program Analysis and Scientific Communication, NIAMDD, will describe the history and current Federal involvement in end-stage renal dialysis, which is a technology that is already far along in widespread clinical use. Then Dr. Robert Ringler, Deputy Director, NHLBI, will discuss the technology assessment of the clinical application of a totally implantable artificial heart, a technology that is in the development stage. For both of these presentations we have tried to avoid entanglement in the interesting questions of "how does it work" and "what about this or that aspect of it in regard to its technical function." We will also hear a report on the Proposed NIH Guidelines on Recombinant DNA Research which engaged some of you when you were on this Committee in February. This is a kind of important technology assessment that is shortly to become part of the responsibilities of this group in the sense of providing an essential interface between the public and science in regard to matters of this sort. We have scheduled a discussion after each of these presentations. I will also call upon the special consultants to share with us information on technology assessment efforts in their respective organizations, for indeed there are a number of organizations within the Government and some without who have already been considering

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for some time the matter of technology assessment. You have in your books summaries, or parts of the chapters, from the report of the committee of the Office of Technology Assessment to which we will have reference as we go along.

With the foregoing review, then the rest of the meeting is going to be devoted to a discussion of the question of how NIH can proceed in discharging its responsibilities whatever they are determined to be, in assessing the impact of new technology. I think that the excerpts of the OTA report which are in your book, especially Chapter 4, are especially useful and thoughtful analyses on some methods for conducting technology assessment. I believe it will be helpful for us to keep in mind during our discussions the questions that are posed in Chapter 4, namely; how is it that the medical technologies can be selective for assessments?; how will the assessment be conducted?; and how will the results of the assessment be used? In considering these questions we must especially keep in mind the limits of technology assessment, and the questions as to whether a technology can be assessed and whether it is worth doing. So the task before us today as posed in the letter from Senator Javits and as posed by the OTA Report, is to determine the scope of responsibility of the NIH and within that responsibility some framework for dealing with this still somewhat abstract problem of technology assessment. We need to come forth with the beginnings of strategy. A number of possible strategies are suggested in the letter from Senator Javits and in the OTA Report. I need to emphasize to some of you that

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the NIH, through its advisory committee structure, does consider issues that are relevant to technology assessment. As the OTA report points out, this Committee can, and will, play an important role in this regard. They have identified this Committee on which you sit as doubtless having an important role. That role was played in an extraordinary fashion in February when some of you met with the special committee consisting of many ad hoc consultants to deal with the question of the NIH Guidelines on Recombinant DNA Research. At that meeting a public hearing was held which allowed the widest opportunity for comment and assessment of the proposed guidelines. It was a model for such review and consideration and we need to pursue it and others to assure that the National Institutes of Health meets the challenges and fulfills its social responsibilities. And I think today is a most important beginning for such review.

If there are no questions about the agenda or what we propose to do, I think that we will begin precisely on schedule and we will call upon Dr. Ben Burton at this time from the National Institute of Arthritis, Metabolic Diseases, Diabetes, Digestive Disorders, and other problems, including kidney disease, to give us a description of the first of the three examples that we have selected for consideration. This first example is fully developed, its implications and history can be examined from an interesting vantage point. It will be followed by a more shadowy, but even larger problem relating to chronic replacement of the human heart.

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We have asked Dr. Burton to limit his presentation to 45 minutes to be followed by discussion. However, we will want to continue in an informal mode and may interrupt Dr. Burton at any time on a question of substance.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

STATEMENT BY

DONALD S. FREDRICKSON, M.D.
DIRECTOR, NATIONAL INSTITUTES OF HEALTH

BEFORE THE

SUBCOMMITTEE ON HEALTH
COMMITTEE ON LABOR AND PUBLIC WELFARE
UNITED STATES SENATE

June 17, 1976

Mr. Chairman and Members of the Subcommittee:

I am especially pleased to participate in this series of Hearings on basic issues in biomedical research.

Just two months ago, a prestigious group completed a 15-month study of biomedical and behavioral research, and made its report to the Congress, the Executive Branch, and the public. This was the President's Biomedical Research Panel--created by Public Law 93-352; and its conclusions and recommendations were submitted on April 30.

The charge to the Panel was to review, assess, and make recommendations concerning biomedical and behavioral research conducted and supported by the National Institutes of Health and the National Institute of Mental Health, with respect to program content, organization, and operation. In so doing, the Panel, in its own words, "conducted an extensive study [involving] assessments of the state of the science, the impact of federally funded research on institutions of higher education, the organization and management of the NIH and the ADAMHA, the dissemination and application of research findings, and the development of policy for Federal support of biomedical and behavioral research." To these tasks the Panel, in aggregate, brought management insights as well as biomedical expertise.

Doubtless it is too soon to evaluate how useful its report will prove to be. But this was a distinguished and diligent effort to deal with first-order problems. Its timing was propitious, for it represented the first comprehensive examination of the form and substance of NIH programs since the landmark report of the Wooldridge Committee in 1965.

There are interesting differences between the research assessment tasks adopted by the Wooldridge Committee and those accepted by the President's Panel a decade later. In 1965 the principal (though not the only) concern of the Wooldridge Committee was with the quality of research supported. In 1975 the quality of research was not an issue, though I would add that the so-called "Cluster Reports," prepared at the request of the Panel, contain most useful assessments of the state-of-science in key areas. The main issue for the 1975 Panel was perhaps a new one: how to ensure the effectiveness of biomedical research and keep it responsive to the increasingly diverse and sometimes conflicting needs of the society that underwrites it.

From a personal standpoint, the Panel's deliberations were a helpful adjunct to my own attempts to deal with many of the same issues as I assumed the position of Director, NIH.

I believe the Panel made a strong effort to identify areas in which it could offer practical suggestions to solve problems. The members listened carefully to the agenda of problems and issues which I and other spokesmen of the research community brought to their attention. The range of review was impressive, extending to philosophic as well as scientific issues; and the Panel was selective about where it felt it could exert an influence. Its conclusions and recommendations are, in my view, positive and helpful. Some of the most useful suggestions dealt with the details of the process and mechanisms for research.

The creation of the Panel and its mandate flowed directly from the legislative actions of this Subcommittee. That legislation was a

response to a call for a study of biomedical research which came from many quarters: from supporters and sceptics of research; from other members of Congress and Executive office-holders; from lay and professional groups; from economic modelers, academic officials, and individual scientists.

A major thrust behind this call for a study was uncertainty about how well the national biomedical research effort was being carried out to "achieve practical health goals"--by which was meant principally disease prevention or effective treatment. Another understandable concern was the staggering climb of medical care costs, which continues without remittance. Thus, behind many of the calls for a study of research was the perception of troubles in our health care system and in the Federal role in that system. The contentions, in any case, were serious enough:

- . that new knowledge from the ever-increasing investment in research was not getting to the sick patient in a timely way;
- . that scientists were working on problems that interested them, rather than on problems that the paying public wanted solved;
- . that the research community put out new technologies with no concern for costs, and that research was contributing directly to the rising costs of health care;
- . that Federal research programs brought instabilities and had other harmful impacts on cooperating academic institutions;

- . that processes of priority setting, planning, and evaluation were not sufficiently clear to key Federal agencies;
- . that excessive emphasis on categorical disease areas, especially cancer and heart disease, and on particular mechanisms of support--for example, center grants and contracts--was responsible for imbalance and eroded effectiveness of federally sponsored research; and
- . that the Federal enterprise was not properly organized and managed for cost-effective accomplishment.

Added to this was a whole series of challenges stemming from increased social imperatives. Some of these have to do with citizen interest in governmental processes and social issues. Some have to do with an ever-increasing capacity of science itself to affect natural events. These included sharpened concern for ethics and due process in clinical research; issues of privacy and informed consent in conduct of clinical trials; insistence on openness of decision-making processes; and critical examination of the safety and appropriateness of the conduct and application of certain types of research. None of these concerns has diminished in the ensuing two years, and some have become more urgent. The report of the President's Panel is an important start in addressing these complex problems. I assume that this Committee intends to build on that base.

Mr. Chairman, as Director, NIH, I am in the midst of conflicting views of NIH priorities and responsibilities. I therefore welcome the

forthcoming opportunity to discuss these matters with the Committee. If I may, I should like at this point to try my hand at an appropriate structuring of the main issues in biomedical research. This may make it easier to identify in a systematic way those matters with which the Panel has dealt comprehensively, and thus to isolate remaining areas where our principal attention should be directed. The subject does not lend itself to easy categorization. I will attempt, however, to identify a few broad areas of concern.

Maintaining Effectiveness and Responsiveness of Biomedical Research

First, I think we can all agree that the vigor and productivity of the Nation's biomedical research is a necessary condition for further improvements in the health of our people. Moreover, it seems certain that the Federal Government will continue to be the principal supporter of such research. This is because of the size and nature of the enterprise and its implications for the public investment in purchase of health care services--an investment that is growing in both absolute and relative terms. As public officials we can agree with the Chairman's recent statement that the conquest of diseases has always been the reason for Federal support of research. I would suggest, however, that this goal has been broadened to encompass a whole spectrum of understanding and intervention in genetics and reproduction, in the environment, and in lifestyle and behavior--all directed toward improving the quality as well as the length of the human life span.

With this goal in mind, my concern for maintenance of a vigorous basic research enterprise is rooted in the observation that the major

advances in health care have been dependent on the elucidation of fundamental biological processes; and further, that the often tortuous path from initial research to clinical application is invariably easier to reconstruct than to predict. So, I can discern no ready substitute for reliance on the support of meritorious basic science, coupled with careful selection of applications for development, as the chief source of new approaches to our most baffling health problems. At the same time, I appreciate and share the concerns of those who believe that the limits on available resources and the public's interest in the solution or amelioration of certain problems require a heightened sensitivity to the need for wise choices in the support of research.

Let me discuss very briefly what I regard as the essential conditions for vigorous, productive biomedical research:

Adequate funding. An acceptable definition of what constitutes an adequate Federal investment in research has eluded thoughtful observers for decades. Recognizing that no formula can adequately encompass all the relevant scientific, economic, and social considerations, I would suggest that one reasonable approach might be to consider linking research expenditures to the cost of the Nation's health "industry."

Stable support. A universal characteristic of biomedical research, at any point along the spectrum from fundamental inquiry to clinical application, is that the relationship of planning and execution to the Federal appropriations process--or any short-term funding cycle--is an extraordinarily poor fit. Fluctuation and uncertainty in Federal funding has major implications for our ability to develop coherent programs. Even more dramatic is the impact of fluctuating support on the performing

individuals and institutions. Research has long ceased to be an intermittent pursuit of amateurs. It is a process enhanced by experience and dependent upon continuity. The goals are necessarily long-range, and relative stability is essential to maximum productivity.

I am convinced that resolution of this problem will go a long way toward increasing the return on the Federal investment in research.

Support of excellence. As I indicated earlier, precise identification of areas for research emphasis is a difficult undertaking, particularly for untargeted or basic research. At any given moment, however, it is possible to achieve a reasonable degree of expert consensus on broad areas of need and opportunity--as was done so ably in the Panel's Cluster Reports--as well as to identify individual projects worthy of support. A further refinement of this process, especially important when resources are limited, is the identification of areas and projects of especially high program relevance.

I might note here that the Federal Government, as chief supporter of research, is in a unique position to encourage excellence, particularly through its support of research in academic institutions. In carrying out this role, however, there is a tension between the need to channel support to existing centers of excellence and the need to foster development of similar capabilities in less well-recognized institutions and individuals.

A related issue stemming from concern over scientific excellence and stable support is the appropriate Federal role in support of research training. This, of course, has been much debated in recent years.

While many issues remain unresolved, there has emerged a fair degree of consensus on the need for some Federal support designed to foster high-quality training programs and to intervene where the likelihood is great that the so-called "play of the market" will not yield investigators of kinds or in numbers needed to sustain the research effort. There is agreement too that restoration of stability in support will contribute much to realization of these aims.

Finally, I should like to mention a point of lesser magnitude, but one that has surfaced in almost every examination of NIH programs. Our steadily decreasing ability to compete with private sector salaries for top scientific and medical personnel continues to hamper our ability to engage the finest minds in the direction of federally supported research. And the requirement for top talent in Government science grows with the complexity of the role of Government in science and medicine. I am aware that many diverse concerns contribute to our present dilemma.

The Unity of Bioscience. Biomedical research can be viewed as a mosaic--an art form in which many seemingly unrelated pieces form a unified whole. The organization of the National Institutes of Health rightly reflects the great public interest in the conquest or amelioration of various diseases. Refinements of this organization have recognized the need for support of noncategorical research and investigation into broad areas such as environmental health or human development. In recent years, there has been increasing pressure for expanded efforts in a variety of disease areas. The general thrust of these efforts reflects a perfectly understandable concern for the problems that the paying

public considers most important. At the same time, however, focusing on one piece of the mosaic may retard assemblage of the larger picture, and the relationship of broadly based research to the production of knowledge relevant to specific diseases may be overlooked. It may be that we scientists have not been sufficiently clear in explaining these relationships. I am hopeful that increasing public sophistication, as well as heightened sensitivity on the part of the scientific community, will contribute to more useful dialogue in this area in the years ahead.

Defining the Role of NIH

Thus far I have been concerned with the conditions for successful accomplishment of what, for want of a better term, I will call the "traditional" NIH mission in support of basic research and selected applications. NIH has always been engaged in various activities at the interface of research and health care. The concerns about the health system that I mentioned earlier have given new urgency to the perennial questions about the scope and practical boundaries of the NIH mission. Today we are asking to what extent NIH should assume responsibility for--

- . validation of new and established medical and surgical interventions;
- . assessment of the implications of new findings and their readiness for clinical application;
- . cost containment, where research advances may lead to costly treatments;

. dissemination of research results, beyond traditional channels of scientific communication.

The extent to which biomedical research can be held accountable for the dysfunction of the present-day health delivery system is difficult to assess. For the most part, research programs have been kept free of activities directed at regulation or delivery of health care. But while NIH has focused on its research mission, it has engaged off-and-on for years in "control" or "demonstration" activities designed to improve the translation of research findings into health practice. And as public demands mount for more effective regulation of drugs and environmental hazards, NIH expertise has been sought increasingly.

It seems clear that in the future, NIH and the rest of the scientific community must assume more responsibility for the effect of research on the quality of the health care delivered. The need for accelerating the transfer of new technology across the "interface" between biomedical research and the health care community and systems is a major issue. I am currently exploring possible means for enhancing this process, based on the concept of NIH as a "seller" and the health care system as a "buyer."

An element of urgency is derived from a national determination, largely Government-directed, to increase the cost-effectiveness and efficacy of health care. It is necessary to achieve by diligent effort a raising of the level of scepticism throughout the biomedical-research and health-care systems and an acceptance of a collective responsibility

for the cost-effectiveness and efficacy of interventions already widely accepted in medical practice. Another group of questions, mentioned above, relate to translations of new research findings into health care. Our responsibility is to understand more fully and to improve the somewhat informal system whereby consensus is reached concerning the validity of the interventions arising from our research.

The randomized clinical trial is the leading research instrument to assist in reaching this consensus by which biomedical science arrives at its conclusions. The last three decades have seen considerable and progressive growth in our knowledge of how to conduct clinical trials; in the selection of population size and end-points; in use of placebos and the double-blind methodology; in evaluating costs against the probability of obtaining a usable answer, or any answer at all; and in becoming masters of the awesome power of automated data processing for epidemiologic purposes.

A number of important policy questions arise in connection with NIH support for clinical trials. First, the thrust of the NIH efforts to date has been in the direction of assessment of clinical care that has not yet entered into general practice, rather than a validation of currently accepted medical practices. Trials in the latter instance generally are much more expensive, time-consuming, and controversial, and the extent and nature of NIH responsibility is unclear. However, increasing concern for quality assurance in health care has already brought pressure for more efforts in this area. A reasonable approach, it seems to me, would be to confine NIH efforts of this sort to problems

where there is strong consensus on the need for validation and a lack of interest or capability to conduct such studies elsewhere.

A second and closely related issue is the desirable level of NIH support for clinical trials. These account for approximately 15 percent of the National Heart, Lung, and Blood Institute budget and 8 percent of the National Cancer Institute budget. Implicit is the question of the kind of clinical testing NIH should conduct or support, or more appropriately leave to other agencies or privately supported groups. A clinical trials committee has been established to provide for better central coordination of NIH-funded clinical trials. Perhaps funding for trials should come not only from the research budget but also from alternate sources. In the case of trials of existing medical practices, providers of health care clearly benefit from the findings, and this may also be true for selected cases in which new therapies are being evaluated.

The growing consensus on the need for validation of clinical practices will affect the orientation of health research and service agencies, including NIH. Where there are deficiencies in the substance of medical or psychiatric care, the biomedical and behavioral research communities must expand their activities to include more clinical trials in areas where research has pointed to the feasibility of new interventions. The substantive issues here are scientific and technical, and the answers sought are logical end-points of research. Here again, our concern is with the scope and practical boundaries of the NIH role, rather than the essential nature of our mission.

Another area in which NIH must be prepared to expand its role is

that of technology assessment. We must be ready to examine the growing multiplicity of palliative technologies, such as renal dialysis, in association with the high cost of applying these in present-day clinical settings and the mounting demands that they be extended to every patient in need of them. Science has some burden of anticipating the fruits of its research, but it is unreasonable to expect inquiry along certain avenues to be avoided simply because it might lead to expensive therapies, or "halfway technology," as Lewis Thomas has aptly described it. A formula for compromise, incorporating subtle human and social values as well as scientific concerns, is needed. Anticipation of technological development, and constraint of technology on which a single useful life may depend, are formidable tasks.

The June meeting of the Advisory Committee to the Director, NIH, was devoted to an examination of these questions. The committee reviewed past NIH efforts in renal dialysis, present efforts in the artificial heart, and future efforts in DNA recombinant research. The advice of the committee was sought on what NIH responsibilities can be and should be in this most important area. As part of this effort, the committee focused on broader issues in the hope that social, legal, ethical, and economic concerns would be fully considered.

A related matter which has recently engaged my attention is the role of NIH in dissemination of research results. At this time our principal focus of attention with respect to the dissemination of research information is on the practicing health professional. A major dysfunction in the health care system has been inadequate transfer of

research findings to the health practitioner as well as to the public. Several new approaches are being or will be tested for direct communication to the practicing community, including publication of a two-page monthly research review directed to physicians through the Journal of the American Medical Association, feasibility studies of telephonic consultation services, and experimental use of the Communications Technology Satellite.

Public Interest and Input

These, then, are my major concerns relating to the nature and conduct of the NIH mission. An underlying theme, which I would like to develop further, is the public nature of the research enterprise, in terms of responding to society's need for information that may be applied to health problems, validating those findings, and assuring that new knowledge is translated into improved health care. I am deeply interested in finding ways through which the research process may be made more open to observation and participation by the public.

There are two levels of involvement here. The first, which I would characterize as the "macro" level, has always provided for some public scrutiny and input, primarily in the context of Executive and Congressional processes of resource allocation and oversight. Since the 1950s NIH has been examined by at least 10 Federal and non-Federal commissions. The most notable of these have been the Wooldridge Committee, reporting in 1965, and the President's Biomedical Research Panel. Congressional attention has taken the form of oversight hearings, the setting of time and dollar limits on research program authorizations, and special

mandates. This increased dialogue with the Congress has, I hope, been helpful.)

Further, the passage of broadened freedom-of-information legislation has opened to the public most of the machinery of the research advisory process. Except for certain problems in the peer review system, these moves for increasing public audit of biomedical research are commendable. They demonstrate clearly that research is susceptible to public direction and is in no sense the exclusive province of an unmanageable elite.

On a "micro" level, the NIH has a number of organizational structures that permit public participation in decision making. Public representation is found at all levels of the NIH through the mechanism of advisory councils, all of which have a statutory requirement for lay representation. The Advisory Committee to the Director, NIH, has the potential for providing a functional interface between research, services, and the public interest. The advisory committee is charged with advising the Director, NIH, on matters relating to the broad setting--scientific, technological, and socio-economic--in which the continuing development of the biomedical sciences, education for the health professions, and biomedical communications must take place. The members of the committee are representatives knowledgeable in the fields of basic and clinical biomedical sciences, the social sciences, physical sciences, research, education, and communications. The Director, NIH, has made recommendations to strengthen this committee and enable it to serve better in a role of public oversight. If the committee is to play this vital public interest role, its members must be persons of great capability, vision and understanding.

In addition to these formal mechanisms, there are ad hoc ways in which the NIH can and should seek public participation in its decision-making. The recent deliberations regarding research on recombinant DNA are a case in point. Development of guidelines for this type of research entailed two rather different levels of analysis, both requiring input from a variety of sources:

First, there was the fundamental question of the direction and pace of the research. In addition to technical questions of safety, there emerged a number of concerns related to the ultimate uses of the new knowledge I anticipated from this type of experiment. In the latter instance one's view may be shaped by understanding of scientific possibilities, but fundamentally this and many similar questions are, in Alvin Weinberg's phrase, "trans-scientific." That is, answers to such questions are not derived from hard scientific evidence alone, but depend on ethical, social, or economic judgments as well. The case for public involvement is self-evident.

Second, even after some consensus had been reached with regard to the future direction of recombinant DNA research, there was vigorous disagreement over the necessary safety procedures. Here the principal questions at issue were technical in nature, but individual and community values played an important role.

It seems clear then, that public participation in scientific decision-making will continue to increase. As Director, NIH, I have given high priority to these efforts, and I applaud the work of the Panel and this Subcommittee in encouraging public consideration of so many questions of importance to science and society.

Mr. Chairman, this concludes my prepared statement. I would be happy to discuss any questions that you or other members of the Subcommittee may have.

PRESS CONFERENCE ON DNA GUIDELINES

June 23, 1976

OPENING REMARKS

By

DONALD S. FREDRICKSON, M.D. 1/

Today, with the concurrence of the Secretary of Health, Education, and Welfare, and the Assistant Secretary for Health, I am issuing guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules. The NIH has also undertaken an environmental impact assessment of these guidelines for recombinant DNA research in accordance with the National Environmental Policy Act of 1969. The purpose of this assessment will be to review the environmental effects, if any, of research that may be conducted under the guidelines. The assessment will provide further opportunity for all concerned to address the potential benefits and potential hazards of this important research activity.

I expect a draft of the environmental impact statement to be completed by September 1 for comment by the scientific community, Federal and state agencies, and the general public.

1/ Director, National Institutes of Health, Bethesda, Maryland

These guidelines replace the guidelines issued in 1975 in the Summary Statement of the Asilomar Conference on Recombinant DNA Molecules.

The experiments voluntarily deferred under the Asilomar guidelines are still prohibited by the NIH guidelines. The Asilomar guidelines in many instances permitted certain experiments to proceed under less strict conditions than do the NIH guidelines. The latter define much more explicitly the physical and biological containment conditions designed to protect workers and the environment, while permitting this important line of work to proceed.

The NIH guidelines contain many details concerning safety practices and define the responsibilities of investigators and institutions where the research is to be conducted. Finally, a structure is established for implementation by NIH staff and advisory committees.

Thus, these guidelines are being released prior to the completion of the environmental impact assessment, because they will provide still greater protection for the public and the environment than the current Asilomar guidelines might afford. The NIH guidelines will be in effect while the environmental impact assessment is under way.

As most of you know, approximately two years ago, scientists engaged in recombinant DNA research voluntarily called for a moratorium of certain experiments pending an assessment of potential hazards of this research and the development of appropriate guidelines. In response, the National Institutes of Health and the National Science Foundation supported a

conference sponsored by the National Academy of Sciences which was held at the Asilomar Conference Center in California in February 1975. The consensus of the meeting at Asilomar was that certain experiments should not be done at the present time, but that most of the work on construction of recombinant DNA molecules should proceed with appropriate precautions. The Asilomar Conference report also made interim assessments of the potential risks associated with different types of experiments.

The Asilomar Conference actions led the NIH to establish an advisory committee to develop guidelines for recombinant research funded or conducted by the NIH and to devise programs for assessing and controlling hazards in such research. After a year's work, the committee in December 1975 proposed guidelines for the NIH to govern such DNA recombinant research.

The proposed guidelines were reviewed at a special meeting of the Director's Advisory Committee held at the NIH on February 9-10, 1976. Members of the committee represented areas including not only science, but also law, ethics and consumer affairs. The meeting afforded an opportunity for the scientific community and the public to comment on the proposed guidelines. Over the past several months I reviewed the proposed guidelines in the light of the comments and suggestions made by the participants at the meeting as well as the written comments received after the meeting. A number of issues of special concern to the commentators were reviewed at my request by the advisory committee that developed the guidelines.

I considered carefully the responses of that committee to the issues raised by the commentators. The NIH will publish a report containing the full transcript of the public hearing, the statements filed by public and scientific witnesses and the correspondence addressed to me on this matter. My decision, which is based on that record, examines each of the substantive issues presented with an explanation of my decision on each issue. The guidelines being released today contain a number of revisions based on that analysis.

The NIH guidelines will govern research at laboratories of the NIH and those of its grantees and contractors. On the basis of continuing discussions with other organizations which are conducting, monitoring or supporting this type of research in this country and abroad, we believe these guidelines will be adopted by other laboratories throughout the United States and that they will provide a base for development of similar guidelines in foreign countries.

The NIH recognizes a special obligation to disseminate information on these guidelines as widely as possible. They, and the decision paper accompanying their release, will be published forthwith in the Federal Register for comment. Copies will be distributed to all who have contributed to debate concerning them. Filing of the environmental impact statement will provide further opportunity for the scientific community, Federal, State and local agencies and the general public to address the potential benefits and hazards of this research area.

Beginning tomorrow Dr. Gartland will also be briefing appropriate officials at the World Health Organization, The European Molecular Biology Organization and in Britian. Today the guidelines will also be sent to all science attaches of foreign embassies located in Washington and to U.S. science attaches in our embassies in foreign countries.

These NIH guidelines for conduct of recombinant DNA research represent a small but important step in developing standards and criteria to protect the public interest and to guide the decision-making process required for conservative exploitation of new knowledge that combines profound promise with uncertain hazards.

It is my belief that these guidelines, and the provision of all the information leading to their development and promulgation, constitute a new structure that will usefully serve to improve the quality of public debate and scientific consideration of this exceedingly important matter.

" ... and a time to heal"*

Donald S. Fredrickson, M.D.**

It is a special pleasure for me to participate in these ceremonies marking the opening of the Georgetown University Hospital Concentrated Care Center - and to represent the National Institutes of Health, your neighbor at the other end of Wisconsin Avenue, in extending sincere congratulations to all whose efforts and support have brought the Center into being.

This is the Bicentennial year, and things historical naturally come to mind. The long and distinguished history of Georgetown University began in the same year that George Washington was first elected President. And your engagement in teaching and practicing the healing arts goes back to 1851.

Our two institutions - the NIH and Georgetown - have worked together in many significant and beneficial ways. That collaboration dates back to the time when Dr. Joseph J. Kinyoun was Director of NIH's predecessor organization, the National Hygienic Laboratory. I have some reasons these days to reflect on what has happened to Dr. Kinyoun's office since those simpler

* Presented at the dedication of the Concentrated Care Center of Georgetown University Hospital, Washington, D.C., June 26, 1976.

** Director, National Institutes of Health

days in the 1890's. His primitive NIH was blessed with an appropriation of a few thousand dollars, a hundred or so employees. The entire Office of Management and Budget presumably was represented by the household economies of Mrs. Grover Cleveland. (Grover Cleveland, who was President from 1885-89 and again from 1893-97, married Frances Folsom in the White House during his first term. She was then 22, and he was 49. She lived until 1947. The Encyclopedia Britannica commented: "The Clevelands enjoyed a happy family life despite their disparity in ages.") At that time Congress had little interest in the priorities of the National Hygienic Laboratory or expectations that cancer, dropsy, and colic would be much affected by its puttering. It was a far cry from NIH today with its - 2/3 ? , 14,000, responsibilities

Director Kinyoun not only had time to carry on pioneering research on the uses of the newly discovered Roentgen Rays, he also used to lecture at the Georgetown School of Medicine. One can imagine how delighted Dr. Kinyoun would have been with the extraordinary advances which have been made in the field of radiology since his time. He would have stared in disbelief at a demonstration of computer assisted tomography and in using the ACTA scanner now in place here.

The provision of medical care has been a center of concern of this institution for a century and a quarter. It, like the rest of the western world, has experienced a revolution

brought about by the coupling of science to medicine. Out of all this has come ever-increasing power to sustain life against the extremes of disease or injury.

We have learned that to be near death is not necessarily to die. And in this fact lies reason for rejoicing on this occasion. It also mandates some sober reflection.

In the presence here of so many professionals, I put my amateur standing at risk by engaging in scriptural interpretation.

In Ecclesiastes there is a verse composed, I believe, by Solomon, that contains the phrases:

"To everything there is a season,
And a time to every purpose under the heaven,"

There follows a calendar of human experiences. And here it says there is also "... a time to heal."

These words remind us of the inexorable cycle of life. We have not changed - and we will not ever upset by much that grand design. But man has vastly extended the season for healing. Today we can do much to skip that season. The small-pox virus will shortly be a curiosity. Polio and measles have nearly disappeared. These are blessings which succeeding generations will enjoy as the memory of the holocausts disappear and the genius of invention which eliminated them is no longer remembered.

And, for the patient who is ill - seriously ill - the new powers that can be applied in medical care have expanded the critical hours during which it is possible to bring healing and restoration. Today is "a time to heal" many whose condition would have been considered hopeless just 50, 25 or even 15 years ago

Improved maternal and child care have brought further declines in the infant death rate - last year for the first time since adequate statistics have been available, we had a decline in death from cardiovascular disease.

On the horizon are still more advances. The world is on the threshold of getting effective vaccines against hepatitis, and better ones against influenza seem assured. New understanding of the immune system and tissue compatibilities hold extraordinary promise of revealing innate tendencies toward development of certain diseases that are both common and obscure.

Across the bright face of these prospects, there fall some shadows.

Can these be the extensions of what is referred to in yet another verse from Ecclesiastes:

"For in much wisdom is much grief: and he that increaseth knowledge increaseth sorrow."

This very week you may have read NIH brought to fuller

public attention another example of new techniques of science to change life shadowed by public controversy over those powers.

(Recombinant DNA Research)

There are inevitable tensions at the interface between science and society. So also we have learned that there are unexpected tensions between medicine, other health professions, and some parts of society concerning health practices - their nature, their costs, their value.

The paradoxical dark side of bright new knowledge is our constant companion as we learn new means for drastic interference with natural processes and can stave off physical death for long periods of time. The physician's age-old question - "Can we successfully grapple with death in heroic ways?" has been known of late to change its verb to "may we do so?"

Certainly the most sharply pointed dilemma is faced when our technical ability exceeds the limit of our philosophical wisdom as, for example, in the use of mechanical means which can sustain the body as an organism in the absence of brain function.

With our increasing application of new technical knowledge, there has been an inevitable increase in the number of such tragically incomplete and unsuccessful interventions. This has led to searches for a new definition of death. It is not within

the powers of science to say when life begins or ends. Lacking a Solomon to define by fiat the "time for healing," the family and the physician have turned to the clergy, and the latter, in turn, to the courts and legislative bodies to help them distinguish life from death.

And the whole of society is turning more and more attention to the health care system. A casual look at the Congressional Record reveals a surprising diversity and intensity of interest in health matters. It is no longer unusual for the White House to send formal health messages to the Congress. And it is extremely common for the Congress to pursue the practices, the financing, the unfilled expectations concerning health in lengthy hearings and debate. Federal interest in the subject has grown steadily through successive administrations whatever their political persuasion.

In the Odyssey, Homer said of the Egyptians that "every one in the whole country is a skilled physician." Not so here, thank heaven, although deans have come to think that nearly every undergraduate wants to be one. But there are clear signs of increasing concerns of the American people about health care, concerns that are driven by spiraling costs in ^atime of greater competition for social resources and times of change in ethical and moral values.

Ivan Illich, currently on best seller lists, had many predecessors. One was Montaigne, who authored an essay which is a caricature of the health care system as seen by one segment of the public today. He told of a small and totally isolated village which had avoided all alliances and traffic with the outside world. By mischance a physician visited, fell

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in love with a village maiden, married her and took up residence there, amongst the villagers. In Montaigne's words, "The man first of all began to teach them names of fevers, colds and imposthumes; the seat of the heart, liver and intestines, a science until then utterly unknown to them; and instead of garlic, with which they were wont to cure all manner of diseases, how painful or extreme soever, - he taught them though it were but for a cold, to take strange mixtures, and began to make a trade, not only of their health, but of their lives. They swear ... that since this use of physic they find themselves oppressed with a legion of unaccustomed diseases and that they perceive a general decay of their ancient vigor, and their lives are cut shorter by the half."

It is not only essayists, but some health economists today who deplore the state of our Nation's health. Their analyses have a negative tone in reference to the impact of medical care on health status. Fingers are pointed at the flattening out of life expectancy curves - and the steep upward slope of costs.

A serious weakness in such analyses is their inability to assess the benefits of medical care in terms of relief of disability, fear and discomfort - the deeply personal factors which cannot be reduced to computer language and easily submitted to the calculus of cost and benefit.

To some degree, the criticisms of medical care extend to questioning the value of continuing research. This is not anti-intellectualism, but part of a national anxiety to commit public resources toward immediate social ends. There are pressing needs. Among them, however, remains that of new knowledge, for which investment remains an essential part of the Nation's expenditures. It need not be said again that priorities must be wisely selected and the maximum use made of new knowledge to better the human condition.

It also need not be said again that this Nation's health system is less than perfect. Indeed perfection is not to be found in any nation.

The voluntary system of health care delivery has served the country well but it must respond to new and exceedingly difficult demands. Where excellence in care is unevenly available, where costs are forced upward by inefficient practices or lack of community organization, it is almost inevitable that collective authority will be mobilized in an effort to correct the dysfunction.

The Concentrated Care Center which we dedicate today is as good an example of the paradoxes of our time as any we could pick.

As its doors open, its parent institution - the medical school - must dedicate itself to ever-increasing preventive care, and thus to the proposition that the Concentrated Care Center should remain as empty as possible.

it might
Perhaps eventually/be converted to a student union. -
thoughts that to hospital administrators represent fiscal madness - for full occupancy is equivalent to cost effectiveness.

The realities are such, however, that we will not have to face such conversion in our time. Healing and restoration are commitments and responsibilities that will remain part of the divine intent for man.

The Concentrated Care Center will make it possible to render superb care at the difficult extreme of the health care continuum. It will also permit you efficiently to concentrate the full power of a variety of specialties on complicated problems which though not immediately life threatening, are difficult to cope with in a more traditional setting.

It seems obvious that the design of the Center and your staffing patterns will generate substantial dividends in more highly effective and/efficient nursing care.

The fact that all 160 patient rooms are identical and that nursing and all other vital support can be concentrated on any of them as needed makes possible a high degree of

continuity of care. This continuity is desirable not only for the physician but the patient as well, who normally will be admitted directly to the Center, and remain in the same room with the same professional team caring for him until recovery.

Most impressive to me is the opportunity this flexible facility gives for studies of the organization of health care delivery, particularly that required in the critical struggles. Much is yet to be learned about better ways for applying what is known.

One tends to think of the Center as a tertiary care center only, but the setting you have provided here for emergency service - essentially primary care - will not only be an important community resource but also a magnificent base for your Emergency Care Residency program.

It will be an excellent place for better training. Thorough flight instruction in the open cockpit days often included in its curriculum a practice parachute jump. The purpose was to insure that the trainee could use the life saving silk when it was needed and then without hesitation. It was a drastic but useful exercise because the planes of that day were unreliable - their engines even less so. Today's student pilot seldom sees a parachute, and is not required to wear one, much less practice with it. His safety is the result of improved

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airframe and engine design - and not the result of an improved parachute.

But in the field of health care, for now, it is necessary and prudent that the life saving power of concentrated care be refined to its maximum without distilling away the essence of compassion and kindness. These things must also be taught here. And what is learned can be transmitted to those who must carry new skills into this community and beyond. I am confident that you have traveled far in that direction. It is fortunate to have a place like this where all man's knowledge can be brought to bear upon a struggle with the ultimate.

With apologies to the writer of Ecclesiastes - all new knowledge does not lead to sorrow. It can extend in blessed ways the "time to heal." This is a promise we make as we dedicate this healing place.

WEDNESDAY, JULY 7, 1976



PART II:

DEPARTMENT OF
HEALTH,
EDUCATION, AND
WELFARE

National Institutes of Health



RECOMBINANT DNA
RESEARCH

Guidelines

Recombinant DNA Research

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health RECOMBINANT DNA RESEARCH Guidelines

On Wednesday, June 23, 1976, the Director, National Institutes of Health, with the concurrence of the Secretary of Health, Education, and Welfare, and the Assistant Secretary for Health, issued guidelines that will govern the conduct of NIH supported research on recombinant DNA molecules. The NIH is also undertaking an environmental impact assessment of these guidelines for recombinant DNA research in accordance with the National Environmental Policy Act of 1969.

The NIH Guidelines establish carefully controlled conditions for the conduct of experiments involving the production of such molecules and their insertion into organisms such as bacteria. These Guidelines replace the recommendations contained in the 1975 *Summary Statement of the Asilomar Conference on Recombinant DNA Molecules*. The latter would have permitted research under less strict conditions than the NIH Guidelines.

The chronology leading to the present Guidelines is described in detail in the NIH Director's decision document that follows. In summary, scientists engaged in this research called, in 1974, for a moratorium on certain kinds of experiments until an international meeting could be convened to consider the potential hazards of recombinant DNA molecules. They also called upon the NIH to establish a committee to provide advice on recombinant DNA technology.

The international meeting was held at the Asilomar Conference Center, Pacific Grove, California, in February 1975. The consensus of this meeting was that certain experiments should not be done at the present time, but that most of the work on construction of recombinant DNA molecules should proceed with appropriate physical and biological barriers. The Asilomar Conference report also made interim assignments of the potential risks associated with different types of experiments. The NIH then assumed responsibility for translating the broadly based Asilomar recommendations into detailed guidelines for research.

The decision by the NIH Director on these Guidelines was reached after extensive scientific and public airing of the issues during the sixteen months which have elapsed since the Asilomar Conference. The issues were discussed at public meetings of the Recombinant DNA Molecule Program Advisory Committee (Recombinant Advisory Committee) and the Advisory Committee to the NIH Director. The Recombinant Advisory Committee extensively debated three different versions of the Guidelines during this period.

The Advisory Committee to the NIH Director, augmented with consultants representing law, ethics, consumer af-

fairs and the environment, was asked to advise as to whether the proposed Guidelines balanced responsibility to protect the public with the potential benefits through the pursuit of new knowledge. The many different points of view expressed at this meeting were taken into consideration in the decision.

The NIH recognizes a special obligation to disseminate information on these guidelines as widely as possible. Accordingly, the Guidelines will be sent to all of the approximately 25,000 NIH grantees and contractors. Major professional societies which represent scientists working in this area will also be asked to endorse the Guidelines. The Guidelines will be sent to medical and scientific journals and editors of these journals will be asked to request that investigators include a description of the physical and biological containment procedures used in any recombinant research they report on. International health and scientific organizations will also receive copies of the guidelines for their review.

Filing of an environmental impact statement will provide opportunity for the scientific community, Federal, State and local agencies and the general public to address the potential benefits and hazards of this research area. In order for there to be further opportunity for public comment and consideration, these guidelines are being offered for general comment in the FEDERAL REGISTER. It must be clearly understood by the reader that the material that follows is not proposed rulemaking in the technical sense, but is a document on which early public comment and participation is invited.

Please address any comments on these draft policies and procedures to the Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments should be received by November 1, 1976.

Additional copies of this notice are available from the Acting Director, Office of Recombinant DNA Activities, National Institute of General Medical Sciences, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014.

DONALD S. FREDRICKSON,
Director,

NIH National Institutes of Health.

JUNE 25, 1976.

DECISION OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH TO RELEASE GUIDELINES FOR RESEARCH ON RECOMBINANT DNA MOLECULES

JUNE 23, 1976.

INTRODUCTION

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INTRODUCTION

Today, with the concurrence of the Secretary of Health, Education, and Welfare and the Assistant Secretary for Health, I am releasing guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules (molecules resulting from the recombination in cell-free systems of segments of deoxyribonucleic acid, the material that determines the hereditary characteristics of all known cells). These guidelines establish carefully controlled conditions for the conduct of experiments involving the insertion of such recombinant genes into organisms, such as bacteria. The chronology leading to the present guidelines and the decision to release them are outlined in this introduction.

In addition to developing these guidelines, NIH has undertaken an environmental impact assessment of these guidelines for recombinant DNA research in accordance with the National Environmental Policy Act of 1969 (NEPA). The guidelines are being released prior to completion of this assessment. They will replace the current Asilomar guidelines, discussed below, which in many instances allow research to proceed under less strict conditions. Because the NIH guidelines will afford a greater degree of scrutiny and protection, they are being released today, and will be effective while the environmental impact assessment is under way.

Recombinant DNA research brings to the fore certain problems in assessing the potential impact of basic science on society as a whole, including the manner of providing public participation in those assessments. The field of research involved is a rapidly moving one, at the leading edge of biological science. The experiments are extremely technical and complex. Molecular biologists active in this research have means of keeping informed, but even they may fail to keep abreast of the newest developments. It is not surprising that scientists in other fields and the general public have difficulty in understanding advances in recombinant DNA research. Yet public awareness and understanding of this line of investigation is vital.

It was the scientists engaged in recombinant DNA research who called for a moratorium on certain kinds of experiments in order to assess the risks and devise appropriate guidelines. The capability to perform DNA recombinations, and the potential hazards, had become apparent at the Gordon Research Conference on Nucleic Acids in July 1973. Those in attendance voted to send an open letter to Dr. Philip Handler, President of the National Academy of Sciences, and to Dr. John R. Hogness, President of the Institute of Medicine, NAS. The letter, appearing in *Science* 181, 1114, (1973), suggested "that the Academies

[sic] establish a study committee to consider this problem and to recommend specific actions or guidelines, should that seem appropriate."

In response, NAS formed a committee, and its members published another letter in *Science* 185, 303, (1974). Entitled "Potential Biohazards of Recombinant DNA Molecules," the letter proposed:

First, and most important, that until the potential hazards of such recombinant DNA molecules have been better evaluated or until adequate methods are developed for preventing their spread, scientists throughout the world join with the members of this committee in voluntarily deferring . . . [certain] experiments . . .

Second, plans to link fragments of animal DNAs to bacterial plasmid DNA or bacteriophage DNA should be carefully weighted . . .

Third, the Director of the National Institutes of Health is requested to give immediate consideration to establishing an advisory committee charged with (i) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules; (ii) developing procedures which will minimize the spread of such molecules within human and other populations; and (iii) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

On October 7, 1974, the NIH Recombinant DNA Molecule Program Advisory Committee (hereafter "Recombinant Advisory Committee") was established to advise the Secretary, HEW, the Assistant Secretary for Health, and the Director, NIH, "concerning a program for developing procedures which will minimize the spread of such molecules within human and other populations, and for devising guidelines to be followed by investigators working with potentially hazardous recombinants."

The international meeting proposed in the *Science* article (185, 303, 1974) was held in February 1975 at the Asilomar Conference Center, Pacific Grove, California. It was sponsored by the National Academy of Sciences and supported by the National Institutes of Health and the National Science Foundation. One hundred and fifty people attended, including 52 foreign scientists from 15 countries, 16 representatives of the press, and 4 attorneys.

The conference reviewed progress in research on recombinant DNA molecules and discussed ways to deal with the potential biohazards of the work. Participants felt that experiments on construction of recombinant DNA molecules should proceed, provided that appropriate biological and physical containment is utilized. The conference made recommendations for matching levels of containment with levels of possible hazard for various types of experiments. Certain experiments were judged to pose such serious potential dangers that the con-

ference recommended against their being conducted at the present time.

A report on the conference was submitted to the Assembly of Life Sciences, National Research Council, NAS, and approved by its Executive Committee on May 20, 1975. A summary statement of the report was published in *Science* 188, 991 (1975), *Nature* 225, 442, (1975), and the *Proceedings of the National Academy of Sciences* 72, 1981, (1975). The report noted that "in many countries steps are already being taken by national bodies to formulate codes of practice for the conduct of experiments with known or potential biohazard. Until these are established, we urge individual scientists to use the proposals in this document as a guide."

The NIH Recombinant Advisory Committee held its first meeting in San Francisco immediately after the Asilomar conference. It proposed that NIH use the recommendations of the Asilomar conference as guidelines for research until the committee had an opportunity to elaborate more specific guidelines, and that NIH establish a newsletter for informal distribution of information. NIH accepted these recommendations.

At the second meeting, held on May 12-13, 1975, in Bethesda, Maryland, the committee received a report on biohazard-containment facilities in the United States and reviewed a proposed NIH contract program for the construction and testing of microorganisms that would have very limited ability to survive in natural environments and would thereby limit the potential hazards. A subcommittee chaired by Dr. David Hogness was appointed to draft guidelines for research involving recombinant DNA molecules, to be discussed at the next meeting.

The NIH committee, beginning with the draft guidelines prepared by the Hogness subcommittee, prepared proposed guidelines for research with recombinant DNA molecules at its third meeting, held on July 18-19, 1975, in Woods Hole, Massachusetts.

Following this meeting, many letters were received which were critical of the guidelines. The majority of critics felt that they were too lax, others that they were too strict. All letters were reviewed by the committee, and a new subcommittee, chaired by Dr. Elizabeth Kutter, was appointed to revise the guidelines.

A fourth committee meeting was held on December 4-5, 1975, in La Jolla, California. For this meeting a "variorum edition" had been prepared, comparing line-for-line the Hogness, Woods Hole, and Kutter guidelines. The committee reviewed these, voting item-by-item for their preference among the three variations and, in many cases, adding new material. The result was the "Proposed Guidelines for Research Involving Recombinant DNA Molecules," which were referred to the Director, NIH, for a final decision in December 1975.

As Director of the National Institutes of Health, I called a special meeting of the Advisory Committee to the Director to review these proposed guidelines. The

meeting was held at NIH, Bethesda, on February 9-10, 1976. The Advisory Committee is charged to advise the Director, NIH, on matters relating to the broad setting—scientific, technological, and socioeconomic—in which the continuing development of the biomedical sciences, education for the health professions, and biomedical communications must take place, and to advise on their implications for NIH policy, program development, resource allocation, and administration. The members of the committee are knowledgeable in the fields of basic and clinical biomedical sciences, the social sciences, physical sciences, research, education, and communications. In addition to current members of the committee, I invited a number of former committee members as well as other scientific and public representatives to participate in the special February session.

The purpose of the meeting was to seek the committee's advice on the guidelines proposed by the Recombinant Advisory Committee. The Advisory Committee to the Director was asked to determine whether, in their judgment, the guidelines balanced scientific responsibility to the public with scientific freedom to pursue new knowledge.

Public responsibility weighs heavily in this genetic research area. The scientific community must have the public's confidence that the goals of this profoundly important research accord respect to important ethical, legal, and social values of our society. A key element in achieving and maintaining this public trust is for the scientific community to ensure an openness and candor in its proceedings. The meetings of the Director's Advisory Committee, the Asilomar group, and the Recombinant Advisory Committee have reflected the intent of science to be an open community in considering the conduct of recombinant DNA experiments. At the Director's Advisory Committee meeting, there was ample opportunity for comment and an airing of the issues, not only by the committee members but by public witnesses as well. All major points of view were broadly represented.

I have been reviewing the guidelines in light of the comments and suggestions made by participants at that meeting, as well as the written comments received afterward. As part of that review I asked the Recombinant Advisory Committee to consider at their meeting of April 1-2, 1976, a number of selected issues raised by the commentators. I have taken those issues and the response of the Recombinant Advisory Committee into account in arriving at my decision on the guidelines. An analysis of the issues and the basis for my decision follow.

I. GENERAL POLICY CONSIDERATIONS

A word of explanation might be interjected at this point as to the nature of the studies in question. Within the past decade, enzymes capable of breaking DNA strands at specific sites and of coupling the broken fragments in new combinations were discovered, thus making possible the insertion of foreign genes into viruses or certain cell particles (plas-

mids). These, in turn, can be used as vectors to introduce the foreign genes into bacteria or into cells of plants or animals in test tubes. Thus transplanted, the genes may impart their hereditary properties to new hosts. These cells can be isolated and cloned—that is, bred into a genetically homogeneous culture. In general, there are two potential uses for the clones so produced: as a tool for studying the transferred genes, and as a new useful agent, say for the production of a scarce hormone.

Recombinant DNA research offers great promise, particularly for improving the understanding and possibly the treatment of various diseases. There is also a potential risk—that microorganisms with transplanted genes may prove hazardous to man or other forms of life. Thus special provisions are necessary for their containment.

All commentators acknowledged the exemplary responsibility of the scientific community in dealing publicly with the potential risks in DNA recombinant research and in calling for a self-imposed moratorium on certain experiments in order to assess potential hazards and devise appropriate guidelines. Most commentators agreed that the process leading to the formulation of the proposed guidelines was a most responsible and responsive one. Suggestions by the commentators on broad policy considerations are presented below. They relate to the science policy aspects of the guidelines, the implementation of the guidelines for NIH grantees and contractors, and the scope and impact of the guidelines nationally and internationally.

A. Science policy considerations

Commentators were divided on how best to steer a course between stifling research through excessive regulation and allowing it to continue with sufficient controls. Several emphasized that the public must have assurance that the controls afford adequate protection against potential hazards. In the views of these commentators, the burden is on the scientific community to show that the danger is minimal and that the benefits are substantial and far outweigh the risks.

Opinion differed on whether the proposed guidelines were an appropriate response to the potential benefits and hazards. Several found the guidelines to so exaggerate safety procedures that inquiry would be unnecessarily retarded, while others found the guidelines weighted toward promoting research. The issue was how to strike a reasonable balance—in fact, a proper policy “bias”—between concerns to “go slow” and those to progress rapidly.

There was strong disagreement about the nature and level of the possible hazards of recombinant DNA research. Several commentators believed that the hazards posed were unique. In their view, the occurrence of an accident or the escape of a vector could initiate an irreversible process, with a potential for creating problems many times greater than those arising from the multitude of

genetic recombinations that occur spontaneously in nature. These commentators stress the moral obligation on the part of the scientific community to do no harm.

Other commentators, however, found the guidelines to be adequate to the hazards posed. In their view, the guidelines struck an appropriate balance so that research could proceed cautiously. Still other commentators found the guidelines too onerous and restrictive in light of the potential benefits of this research for medicine, agriculture, and industry. Some felt that the guidelines are perhaps more stringent than necessary given the available evidence on the likelihood of hazards, but supported them as a compromise that would best serve the scientific community and the public at large. Many commentators urged that the guidelines be adopted as soon as possible to afford more specific direction to this research area.

I understand and appreciate the concerns of those who urge that this research proceed because of the benefits and of those who urge caution because of potential hazards. The guidelines issued today allow the research to go forward in a manner responsive and appropriate to hazards that may be realized in the future.

The object of these guidelines is to ensure that experimental DNA recombination will have no ill effects on those engaged in the work, on the general public, or on the environment. The essence of their construction is subdivision of potential experiments by class, decision as to which experiments should be permitted at present, and assignment to these of certain procedures for containment of recombinant organisms.

Containment is defined as physical and biological. Physical containment involves the isolation of the research by procedures which have evolved over many years of experience in laboratories studying infectious microorganisms. P1 containment—the first *physical* containment level—is that used in most routine bacteriology laboratories. P2 and P3 afford increasing isolation of the research from the environment. P4 represents the most extreme measures used for containing virulent pathogens, and permits no escape of contaminated air, wastes, or untreated materials. *Biological* containment is the use of vectors or hosts that are crippled by mutation so that the recombinant DNA is incapable of surviving under natural conditions.

The experiments now permitted under the guidelines involve no known additional hazard to the workers or the environment beyond the relatively low risk known to be associated with the source materials. The additional hazards are speculative and therefore not quantifiable. In a real sense they are considerably less certain than are the benefits now clearly derivable from the projected research.

For example, the ability to produce, through “molecular cloning,” relatively large amounts of pure DNA from the chromosomes of any living organism will

have a profound effect in many areas of biology. No other procedure, not even chemical synthesis, can provide pure material corresponding to particular genes. DNA “probes,” prepared from the clones will yield precise evidence on the presence or absence, the organization, and the expression of genes in health and disease.

Potential medical advances were outlined by scientists active in this research area who were present at the meeting of the Director's Advisory Committee. Of enormous importance, for example, is the opportunity to explore the malfunctioning of cells in complicated diseases. Our ability to understand a variety of hereditary defects may be significantly enhanced, with amelioration of their expression a real possibility. There is the potential to elucidate mechanisms in certain cancers, particularly those that might be caused by viruses.

Instead of mere propagation of foreign DNA, the expression of the genes of one organism by the cell machinery of another may alter the new host and open opportunities for manipulating the biological properties of cells. In certain prokaryotes (organisms with a poorly developed nucleus, like bacteria), this exchange of genetic information occurs in nature. Such exchange explains, for instance, an important mechanism for the changing and spreading of resistance to antibiotics in bacteria. Beneficial effects of this mechanism might be the production of medically important compounds for the treatment and control of disease. Examples frequently cited are the production of insulin, growth hormone, specific antibodies, and clotting factors absent in victims of hemophilia.

Aside from the potential medical benefits, a whole host of other applications in science and technology have been envisioned. Examples are the large-scale production of enzymes for industrial use and the development of bacteria that could ingest and destroy oil spills in the sea. Potential benefits in agriculture include the enhancement of nitrogen fixation in certain plants, permitting increased food production.

While the projected research offers the possibility of many benefits, it must proceed only with assurance that potential hazards can be controlled or prevented. Some commentators are concerned that nature may maintain a barrier to the exchange of DNA between prokaryotes and eukaryotes (higher organisms, with a well-formed nucleus)—a barrier that can now be crossed by experimentalists. They further argue that expression of the foreign DNA may alter the host in unpredictable and undesirable ways. Conceivable harm could result if the altered host has a competitive advantage that would foster its survival in some niche within the ecosystem. Other commentators believe that the endless experiments in recombination of DNA which nature has conducted since the beginning of life on the earth, and which have accounted in part for the evolution of species, have most likely involved exchange of DNA between widely disparate species. They

argue that prokaryotes such as bacteria in the intestines of man do exchange DNA with this eukaryotic host and that the failure of the altered prokaryotes to be detected attests to a sharply limited capacity of such recombinants to survive. Thus nature, this argument runs, has already tested the probabilities of harmful recombination and any survivors of such are already in the ecosystem. The fact is that we do not know which of the above-stated propositions is corrected.

The international scientific community, as exemplified by the Asilomar conference and the deliberations attendant upon preparation of the present guidelines, has indicated a desire to proceed with research in a conservative manner. And most of the considerable public commentary on the subject, while urging caution, has also favored proceeding. Three European groups have independently arrived at the opinion that recombinant DNA research should proceed with caution. These are the Working Party on Experimental Manipulation of the Genetic Composition of Micro-Organisms, whose "Ashby Report" was presented to Parliament in the United Kingdom by the Secretary of State for Education and Science in January 1975; the Advisory Committee on Medical Research of the World Health Organization, which issued a press release in July 1975; and the European Molecular Biology Organization Standing Committee on Recombinant DNA, meeting in February 1976.

There is no means for a flat proscription of such research throughout the world community of science. There is also no need to attempt it. It is likely that the evaluation engendered in the preparation and application of these guidelines will lead to beneficial review of some of the containment practices in other work that is not technically defined as recombinant DNA research.

Recombinant DNA research with which these guidelines are concerned involves microorganisms such as bacteria or viruses or cells of higher organisms growing in tissue culture. It is extremely important for the public to be aware that this research is not directed to altering of genes in humans although some of the techniques developed in this research may have relevance if this is attempted in the future.

NIH recognizes its responsibility to conduct and support research designed to determine the extent to which certain potentially harmful effects from recombinant DNA molecules may occur. Among these are experiments, to be conducted under maximum containment, that explore the capability of foreign genes to alter the character of host or vector, rendering it harmful, as through the production of toxic products.

Given the general desire that no rare and unexpected event arising from this research shall cause irreversible damage, it is obvious that merely to establish conservative rules of conduct for one group of scientists is not enough. The precautions must be uniformly and unanimously observed. Second, there

must be full and timely exchange of experiences so that guidelines can be altered on the basis of new knowledge. The guidelines must also be implemented in a manner that protects all concerned—the scientific workers most likely to encounter unexpected hazards and all forms of life within our biosphere. The responsibility of the scientists involved is as inescapable and extreme as is their opportunity to beneficially enrich our understanding.

B. Implementation considerations within the NIH

All the commentators had suggestions concerning the structure and function of decision making as it relates to the principal investigator, the local biohazards committee, the peer review group, and the NIH Recombinant Advisory Committee. These comments and my response on the section of the guidelines relating to roles and responsibilities of investigators, their institutions, and the National Institutes of Health are presented below.

Of considerable concern to all commentators was the process by which NIH would proceed to implement the guidelines. The scientific community generally urged that there be no Federal regulations, while some of the public commentators recommended the regulatory process.

Many who opposed changing the proposed guidelines into Federal regulations expressed concern for flexibility and administrative efficiency, which could best be achieved, in their view, through voluntary compliance. Other commentators, however, believed it imperative to proceed toward regulation. In their view, the guidelines could be implemented for purposes of NIH funding and would govern the conduct of experiments until regulations were in effect. Another commentator who thought regulation would be harmful rather than helpful suggested that if there were to be regulations, they should be along lines similar to those that govern the sale, distribution, use, and disposal of radioisotopes.

The question of how best to proceed now that the guidelines have been released deserves careful attention. I share the concern of those who feel that the guidelines must remain flexible. It is especially important that there be opportunity to change them quickly, based on new information relating to scientific evidence, potential risks, or safety aspects of the research program.

The suggestions for regulation need further attention at this time. The process for regulation not only involves the Director of NIH, but also the Assistant Secretary for Health and the Secretary of Health, Education, and Welfare. These guidelines are being promulgated now in order to afford additional protection to all concerned. Consideration of their conversion to regulations can proceed with continuing review of their content and present and future implications. Meanwhile, the NIH shall continue to provide the opportunity for public comment and participation at least

equivalent to that provided if steps towards regulations were to proceed immediately. The guidelines will be published in the FEDERAL REGISTER forthwith to allow for further public comment.

C. Implementation considerations beyond the purview of NIH

Special concern has been expressed by many commentators regarding the application of the guidelines to research outside NIH by investigators other than its grantees or contractors. It has been urged that the guidelines be made applicable to recombinant DNA research conducted or supported by other agencies in HEW and by NSF, ERDA, DoD, and other governmental departments. Most commentators believe that these or similar guidelines should also govern research in the private sector, including industry, voluntary organizations, and foundations. Many feel that experiments conducted in colleges, universities, and even in high schools require some form of monitoring. And finally, all agree that in view of the potential hazards of recombinant DNA research to the biosphere, some form of international understanding on guidelines for the research is essential.

The committee, in the proposed guidelines, has suggested as one means of control that a description of the physical and biological containment procedures practiced in a research project be included in the publication of research results. In the scientific community this can be a powerful force for conformity, and we will undertake to present the recommendation to all appropriate journals. We are also prepared to take steps to disseminate the guidelines widely, and to arrange for a continual flow of information outward concerning the activities of the Recombinant Advisory Committee and the Advisory Committee to the Director, NIH, in the evolution of the guidelines and their implementation.

In response to these suggestions, I have already held a meeting with relevant HEW agencies and with representatives from other departments of the Federal Government. The purpose of the meeting was to exchange information on recombinant DNA research and to discuss the NIH guidelines. It served as an important beginning to address a common concern of these public institutions. A number of the representatives indicated that various departments might very well adopt the guidelines for research conducted both in-house and supported outside. Following up, I have begun preliminary discussions with the Assistant Secretary for Health and the Secretary of HEW, to determine possible methods to ensure adoption of the guidelines by all Federal agencies. Encouraged by these efforts, we held a meeting on June 2 with representatives of industry to provide them with full information about the guidelines and to help determine the present and future interests of industrial laboratories in this type of research. The meeting provided one of the first opportunities for industry representatives to convene for a discussion of this research area, and an industry com-

mittee under the auspices of the Pharmaceutical Manufacturers Association will be formed to review the guidelines for potential application to the drug industry. Further meetings will be scheduled with other groups that have an active interest in recombinant DNA research.

It is my hope that the guidelines will be voluntarily adopted and honored by all who support or conduct such research throughout the United States, and that at least very similar guidelines will obtain throughout the rest of the world. NIH places the highest priority on efforts to inform and to work with international organizations, such as the World Health Organization and the International Council of Scientific Unions, with a view to achieving a consensus on safety standards in this most important research area.

There has been considerable international cooperation and activity in the past, and I expect it to continue in the future. The aforementioned Ashby Report, presented to Parliament in January 1975, describes the advances in knowledge and possible benefits to society of the experiments involving recombinant DNA molecules, and attempts to assess the hazards in these techniques. The Asilomar meeting also had a number of international representatives, as mentioned previously. The European Molecular Biology Organization (EMBO) has been involved in considering guidelines for recombinant DNA research. They have closely followed the activities of NIH, and will thus be encouraged, I believe, to monitor their research with augmented cooperation and coordination. For example, EMBO recently announced plans for a voluntary registry of recombinant DNA research in Europe. Following this EMBO initiative, NIH shall similarly maintain a voluntary registry of investigators and institutions engaged in such research in the United States. Plans for establishing this registry are under way.

D. Environmental policy considerations

A number of commentators urged NIH to consider preparing an environmental impact statement on recombinant DNA research activity. They evoked the possibility that organisms containing recombinant DNA molecules might escape and affect the environment in potentially harmful ways.

I am in full agreement that the potentially harmful effects of this research on the environment should be assessed. As discussed throughout this paper, the guidelines are premised on physical and biological containment to prevent the release or propagation of DNA recombinants outside the laboratory. Deliberate release of organisms into the environment is prohibited. In my view, the stipulated physical and biological containment ensures that this research will proceed with a high degree of safety and precaution. But I recognize the legitimate concern of those urging that an environmental impact assessment be done. In view of this concern and ensuing pub-

lic debate, I have reviewed the appropriateness of such an assessment and have directed that one be undertaken.

The purpose of this assessment will be to review the environmental effects, if any, of research that may be conducted under the guidelines. The assessment will provide further opportunity for all concerned to address the potential benefits and hazards of this most important research activity. I expect a draft of the environmental impact statement should be completed by September 1 for comment by the scientific community, Federal and State agencies, and the general public.

It should be noted that the development of the guidelines was in large part tantamount to conducting an environmental impact assessment. For example, the objectives of recombinant DNA research, and alternate approaches to reach those objectives, have been considered. The potential hazards and risks have been analyzed. Alternative approaches have been thoroughly considered, to maximize safety and minimize potential risk. And an elaborate review structure has been created to achieve these safety objectives. From a public policy viewpoint, however, the environmental impact assessment will be yet another review that will provide further opportunity for the public to participate and comment on the conduct of this research.

II. METHODS OF CONTAINMENT

Comments on the containment provisions of the proposed guidelines were directed to the definition of both physical and biological containment and to the safety and effectiveness of the prescribed levels. Several commentators found the concept of physical containment imprecise and too subject to the possibility for human error. Others questioned the concept of biological containment in terms of its safety and purported effectiveness in averting potential hazards. The commentators were divided on which method of containment would provide the most effective and safe system to avoid hazards. Several suggested that each of the physical containment levels be more fully explained.

W. Emmett Barkley, Ph.D., Director of the Office of Research Safety, National Cancer Institute, was asked to review the section on physical containment in light of these comments. Dr. Barkley convened a special committee of safety and health experts, who met to consider not only this section of the guidelines but also the section on the roles and responsibilities of researchers and their institutions. The committee thoroughly reviewed the section on physical containment and recommended a number of changes. The Recombinant Advisory Committee, meeting on April 1-2, 1976, reviewed the recommendations of the Barkley group. These are incorporated, with editorial revisions, in the final version of the guidelines.

The present section on physical containment is directly responsive to those commentators who asked for greater de-

tail and explanation. Although different in detail, the four levels of containment approximate those given by the Center for Disease Control for human etiologic agents and by the National Cancer Institute for oncogenic viruses. For each of the proposed levels, optional items have been excluded, and only those items deemed absolutely necessary for safety are presented. Necessary facilities, practices, and equipment are specified. To give further guidance to investigators and their institutions, a supplement to the guidelines explains more fully safety practices appropriate to recombinant DNA research. And a new section has been added to ensure that shipment of recombinant DNA materials conforms, where appropriate, to the standards, prescribed by the U.S. Public Health Service, the Department of Transportation, and the Civil Aeronautics Board.

The section on physical containment is carefully designed to offer a constructive approach to meeting potential hazards for recombinant experiments at all levels of presumed risk. Certain commentators had suggested that the first level of physical containment (P1) be merged with the second level (P2). This suggestion, however, would tend to apply overly stringent standards for some experiments and might result in a lowering of standards necessary at the second level. I believe the level of control must be consistent with a reasonable estimate of the hazard; and the section on physical containment does provide this consistency. Accordingly, the first and second levels of physical containment remain as separate sections in the guidelines.

Because of the nature and operation of facilities required for experiments to be done at the fourth level of containment (P4), a provision has been included that the NIH shall review such facilities prior to funding them for recombinant DNA studies. The situation merits the special attention of experts who have maximum familiarity with the structure, operation, and potential problems of P4 installations. Several commentators advocated that NIH arrange for sharing of P4 facilities, both in the NIH intramural program and in institutions supported through NIH awards. In response to these suggestions, we are currently reviewing our facilities, including those at the Frederick Cancer Research Center (Fort Detrick), to determine how such a program can best be devised. It is most important that P4 facilities be made available to investigators. It should be noted that incidents of infection by even the most highly infectious and dangerous organisms are extremely infrequent at P4 facilities, and therefore the potential for hazard in certain complex experiments in recombinant DNA research is considerably reduced.

III. PROHIBITED EXPERIMENTS

1. Practically all commentators supported the present prohibition of certain experiments. There were suggestions for a clearer definition of the prohibition of certain experiments where increased antibiotic resistance may result. And it

was urged by some that the prohibition be broadened to include experiments that result in resistance to any antibiotic, irrespective of its use in medicine or agriculture. Consideration of such a suggestion must take into account that antibiotic resistance occurs naturally among bacteria, and that resistance is a valuable marker in the study of microbial genetics in general, and recombinants in particular.

In view of these concerns, however, the Recombinant Advisory Committee was asked to reconsider carefully the prohibition and related sections concerning antibiotic resistance. The committee noted that the prohibition relating to drug resistance was intended to ban those experiments that could compromise drug use in controlling disease agents in veterinary as well as human medicine and this is now clearly stated.

In the draft guidelines there were two statements concerning resistance to drugs which related to experiments with *E. coli*. The statements appeared to allow experiments that would extend the range of resistance of this bacterium to therapeutically useful drugs and disinfectants, and thus seemed to be in conflict with the general prohibition on such research. There are numerous reports in the scientific literature indicating that *E. coli* can acquire resistance to all antibiotics known to act against it. Since *E. coli* acquires resistance naturally, the prohibition directed against increasing resistance does not apply. The ambiguous statements have been deleted from the present guidelines. On the other hand, new language has been inserted in the section dealing with other prokaryote species to set containment levels for permitted experiments.¹

2. The Recombinant Advisory Committee was also asked to clarify whether the prohibition of use of DNA derived from pathogenic organisms (those classified as 3, 4, and 5 by the Center for Disease Control, USPHS) also included the DNA from any host infected with these organisms. The committee explained that this prohibition did extend to experiments with cells known to be so infected. To avoid misunderstanding, the prohibition as now worded includes such cells. In addition, the prohibitions have been extended to include moderate-risk oncogenic viruses, as defined by the National Cancer Institute, and cells known to be infected with them.

3. Two other issues relating to the section on prohibited experiments were raised by Roy Curtiss III, Ph.D., Professor, Department of Microbiology, University of Alabama School of Medicine, Birmingham, who is a member of the Recombinant Advisory Committee. Dr. Curtiss noted that for the class of experiments prohibited on the basis of production of highly toxic substances, only

substances from micro-organisms were cited as examples. He suggested that other examples be included, such as venoms from insects and snakes. The committee approved the suggestion and I concur.

In the proposed guidelines, release of organisms containing recombinant DNA molecules into the environment was prohibited unless a series of controlled tests had been done to leave no reasonable doubt of safety. Dr. Curtiss felt that the guidelines should provide greater specificity for testing and should include some form of review prior to release of the organism. I have decided that the guidelines should, for the present, prohibit any deliberate release of organisms containing recombinant DNA into the environment. With the present limited state of knowledge, it seems highly unlikely that there will be in the near future, any recombinant organism that is universally accepted as being beneficial to introduce into the environment. When the scientific evidence becomes available that the potential benefits of recombinant organisms, particularly for agriculture, are about to be realized, then the guidelines can be altered to meet the needs for release. It is most important that the potential environmental impact of the release be considered.

IV. PERMISSIBLE EXPERIMENTS: *E. COLI*-12 HOST-VECTOR SYSTEMS

The continued use of *E. coli* as a host has drawn considerable comment, including some suggestions that its use be prohibited presently or within a specified time limit. It should be stressed that the use of *E. coli* as detailed in the guidelines is limited to *E. coli* K-12, a strain that has been carried in the laboratory for decades and does not involve the use of any strain of *E. coli* that is freshly isolated from a natural source. *E. coli* K-12 does not usually colonize the normal bowel, even when given in large doses, and exhibits little if any multiplication while passing through the alimentary canal. For years it has been the subject of more intense investigation than any other single organism, and knowledge of its genetic makeup and recombinant behavior exceeds greatly that pertaining to any other organism. I believe that because of this experience, *E. coli* K-12 will provide a host-vector system that is safer than other candidate microorganisms.

NIH recognizes the importance of supporting the development of alternative host-vector systems (such as *B. subtilis*, which has no ecological niche in man) and will encourage such development. It should be noted, however, that for each new host-vector system, the same questions of risk from altered properties attendant upon the presence of recombinant genes will apply as apply to *E. coli*. NIH does not believe it wise to set a time limit on replacement of *E. coli* systems by other organisms.

There were specific suggestions concerning the three levels of biological containment prescribed for use of *E. coli* K-12 host-vectors. Some commentators requested a more detailed explanation of

the adequacy of protection for laboratory personnel with the first level of containment (EK1).² Sections of the guidelines dealing with physical containment and roles and responsibilities now specify the need for safety practices and accident plans.

For the second level of containment (EK2), it is required that a cloned DNA fragment be contained in a host-vector system that has no greater than a 10⁻⁴ probability of survival in a nonpermissive or natural environment. It was suggested that the selection of this level of biological containment and the appropriate tests for verification be more fully explained in the guidelines. The committee, in responding to a request for further examination of this point, reviewed at considerable length the testing for an EK2 system and recommended certain modifications. We have accepted the committee's new language that better explains testing of survival of a genetic marker carried on the vector, preferably on an inserted NDA fragment.

Possible tests to determine the level of biological containment afforded by these altered host-vector systems are outlined in this section. Because this is such a new area of scientific research and development, however, it is inappropriate to standardize such testing at the present time. Standards will gradually be set as more experience with EK2 host-vector systems is acquired. The committee, for example, during its April 1976 meetings gave its first approval to an EK2 host-vector system. What is necessary is that new and more effective tests be devised by investigators, and this effort is very likely to occur under the present guidelines. For example, one task recognized by the committee is to clarify how survival of the organism and the cloned DNA should be defined in terms of temperature, medium, and other variables.

It is also very important to note here that the stringent requirements set by the committee for EK2 biological containment jeopardize considerably the capacity of such crippled organisms to survive and replicate even under permissive laboratory conditions. More experience will be required to determine whether EK2 containment will permit some lines of important research to be followed.

Several commentators suggested that methods and procedures to confirm an

¹The EK1 system presently consists of a battery of different vectors and of *E. coli* K-12 mutants, all of which afford a considerable degree of biological containment. The diversity of vectors and of host mutants in this battery has permitted a wide range of important scientific questions to be attacked. For example, the availability of different vectors with cleavage sites for different restriction endonucleases have increased the kind of DNA segments that can be cloned. By contrast, the first EK2 host-vector systems are only now being considered by the Recombinant Advisory Committee. While NIH is supporting the development of more EK2 host-vector systems, it is not expected that a battery equivalent to that available for the EK1 system will be certified by the Recombinant Advisory Committee in the near future.

²Specifically, experiments that would extend resistance to therapeutically useful drugs must use P3 physical containment plus a host-vector comparable to EK1, or P2 containment plus a host-vector comparable to EK2.

EK system at the third level of containment (EK3) be more fully explained. The Recombinant Advisory Committee was asked to consider this suggestion. After considerable discussion the committee declined to define the procedures more fully at this time, because development of an EK3 system is still far enough in the future not to warrant specific testing procedures. Further, it is not clear what tests are best suited. The language, therefore, remains general. The committee, however, is aware of the concerns for a more completely defined system of testing, and has considered the possibility of organizing a symposium for purposes of designating tests. In my view, more fully developed protocols for testing EK3 systems are warranted, and it is necessary that guidelines here be more fully developed before the committee proceeds to certify such a system. In this regard the NIH is prepared through the National Institute of Allergy and Infectious Diseases to support contracts to accomplish this task. We will seek the advice and assistance of the committee to define the scope of necessary work.

These guidelines also include a statement that for the time being no EK2 or EK3 host-vector system will be considered *bona fide* until the Recombinant Advisory Committee has certified it. I share the concern of the commentators that new host-vector systems require the highest quality of scientific review and scrutiny. At this early stage of development, it is most important that the committee provide that scrutiny. Further, I believe that until more experience has been gained, the committee should encourage and the NIH support research that will independently confirm and augment the data on which certification of EK2 host-vector systems are based.

V. CLASSIFICATION OF EXPERIMENTS USING THE *E. COLI* K-12 CONTAINMENT SYSTEMS

The guidelines assign different levels of containment for experiments in which DNA from different sources is to be introduced into an *E. coli* K-12 host-vector system. The variation is based on both facts and assumptions. There are some prokaryotes (bacteria) which constantly exchange DNA with *E. coli*. Here it is assumed that experimental conditions beyond those obtained in careful, routine microbiology laboratories are superfluous, because any exchange experiments have undoubtedly been performed already in nature.

In every instance of artificial recombination, consideration must be given to the possibility that foreign DNA may be translated into protein (expressed), and also to the possibility that normally repressed genes of the host may be expressed and thus change, undesirably, the characteristics of the cell. It is assumed that the more similar the DNAs of donor and host, the greater the probability of expression of foreign DNA, or of possible derepression of host genes. In those cases where the donor exchanges DNA with *E. coli* in nature, it is unlikely that recombination experiments will create new genetic combinations.

When prokaryote donors not known to exchange DNA with *E. coli* in nature are used, however, there is a greater potential for new genetic combinations to be formed and be expressed. Therefore, it is required that experiments involving prokaryotic DNA from a donor that is not known to exchange DNA with *E. coli* in nature be carried out at a higher level of containment. Recombination using prokaryotic DNA from an organism known to be highly pathogenic is prohibited.

There are only limited data available concerning the expression of DNA from higher forms of life (eukaryotes) in *E. coli* (or any other prokaryote). Therefore, the containment prescriptions for experiments inserting eukaryotic DNA into prokaryotes are based on risks having quite uncertain probabilities.

On the assumption that a prokaryote host might translate eukaryotic DNA, it is further presumed that the product of that foreign gene would be most harmful to man if it were an enzyme, hormone, or other protein that was similar (homologous) to proteins already produced by or active in man. An example is a bacterium that could produce insulin. Such a "rogue" bacterium could be of benefit if contained, a nuisance or possibly dangerous if capable of surviving in nature. This is one reason that the higher the phylogenetic order of the eukaryote, the higher the recommended containment, at least until the efficiency of expression of DNA from higher eukaryotes in prokaryotes can be determined.

There is a second, more concrete reason for scaling containment upward as the eukaryote host becomes similar to man. This is the concern that viruses capable of propagating in human tissue, and possibly causing diseases, can contaminate DNA, replicate in prokaryote hosts and infect the experimentalist. Such risks are greatest when total DNA from donor tissue is used in "shotgun" recombinant experiments; it diminishes to much lower levels when pure cloned DNA is used.

The commentators were clearly divided on the classification of containment criteria for different kinds of recombinant DNAs. Many commentators considered the guidelines too stringent and rigid. Others viewed the guidelines in certain instances as too permissive. And still others endorsed the guidelines as sensible and reasonable, affording the public an enormous degree of protection from the speculative risks. Several suggestions were made for the specific classes of experiments, and they follow:

1. Comment on the use of DNA from animals and plants in recombinant experiments varied widely. Some commentators suggested banning the use of DNA from primates, other mammals, and birds. Others suggested that higher levels of containment be used for all such experiments. Still others believed that the guidelines were too strict for experiments of this class. I have carefully reviewed the issues raised by the commentators and the responses of the committee to certain queries concerning use

of animal and plant DNA in these experiments.

In my view, the classification for the use of DNA from primates, other mammals, and birds is appropriate to the potential hazards that might be posed. The physical and biological containment levels are very strict. For example, biological containment levels are at EK2 or EK3, and will effectively preclude experimentation until useful EK2 and EK3 systems are available. EK2 systems are still in the initial stages of development, and the first system was only certified at the most recent meeting of the Recombinant Advisory Committee. An EK3 host-vector system has yet to be tested, and its certification is far enough in the future to place a moratorium on those experiments requiring biological containment at an EK3 level. The physical containment levels of P3 or P4 themselves afford a very high degree of protection. I am satisfied that the guidelines demonstrate the caution and prudence that must govern the conduct of experiments in this category.

The guidelines allow reduced containment levels for primate DNA when it is derived from embryonic tissue or germ-line cells. This is based on evidence that embryonic material is less likely to contain viruses than is tissue from the adult. Obviously, the embryonic tissue must be free of adult tissue, and the present guidelines so indicate.

I have also carefully considered the special concerns arising from the use of DNA from cold-blooded vertebrates and other cold-blooded animals, because several commentators questioned the basis of lower physical and biological containment levels for DNA from these species. The Recombinant Advisory Committee has debated this extensively, and they were asked to do so once again in April.² The committee has now recommended high containment levels (P3+EK2) when the DNA is from a cold-blooded vertebrate known to produce a potent toxin. That recommendation is included in the present guidelines. Where no toxin is involved the committee supported lower

² A committee member, David S. Hogness, Ph. D., Professor, Department of Biochemistry, Stanford University, California, submitted a statement in support of lower containment levels based on current scientific evidence. That evidence is based on certain differences between cold- and warm-blooded vertebrates. One of the criteria used for the evaluation of the relative risk that might be encountered with different levels of shotgun experiment is the degree of sequence homology between the DNA of the given species and that of humans. This criterion is used to estimate the likelihood that segments of DNA from the given species might be integrated into the human genome by recombination; the greater the homology, the greater the likelihood of integration. Studies of sequence homologies indicate that there is a considerable degree of homology between human DNA and DNA from other primates, much less homology between primates and other mammals, and even lower but detectable homology between birds and primates. By contrast, no significant homologies between cold-blooded vertebrates and primates have been detected.

containment levels. The guidelines specify P2+EK2 levels for such work. There was considerable discussion concerning the advisability of recommending lower containment (P2+EK1) when the DNA is isolated from embryonic tissue or germ-line cells from cold-blooded vertebrates. Those supporting lower containment levels argued that the justification for P2+EK2 was the possibility that cold-blooded vertebrates may carry viruses and that the distinction between adult and germ-cell tissue is real. Others argued that, contrary to the situation with primate DNA, viruses are not a central problem with cold-blooded vertebrates and therefore no distinction should be made on the basis of tissue origin. Finally, the committee recommended, on a divided vote (8 to 4), to adopt P2+EK1 when the cold-blooded vertebrate DNA is isolated from embryonic tissue or germ-line cells. Upon reviewing these considerations, I have decided to retain the containment levels for embryonic or germ-line DNA from cold-blooded vertebrates as recommended by the committee.

In April the committee also reviewed, at our request, the classification of experiments where DNA is derived from other cold-blooded animals or lower eukaryotes. Several commentators, for example, had been concerned about the fact that insects are known to carry agents pathogenic to man. In the committee review, it was noted that viruses carried by insects and known to transmit disease to man are RNA rather than DNA viruses and do not reproduce via DNA copied from RNA. In order, however, to make the intent clearer, the guidelines have been rewritten for experiments of this class. New language is inserted to ensure that strict containment levels are employed when the DNA comes from known pathogens or species known to carry them. Further, to reduce the potential hazards, we have also included in the guidelines the requirement that any insect must be grown under laboratory conditions for at least 10 generations prior to its use as a DNA source.

2. As alluded to above, certain commentators expressed concern that when *E. coli* becomes the host of recombinant DNA from prokaryotes with which DNA is not usually exchanged, there is hazard of altered host characteristics resulting from translation of the DNA into functioning proteins. The committee was asked to review the guidelines and take into account this potential hazard. They agreed that the containment levels should be increased for this category of experiment, from P2+EK1 to either P2+EK2 or P3+EK1. That recommendation is included in the present guidelines.

Comments were made concerning that class of experiments in which the recombinant DNA, regardless of source, has been cloned. A clone is a population of cells derived from a single cell and therefore all the cells are presumed to be genetically identical. As outlined in the proposed guidelines, clones could be used at lower containment levels if they had

been rigorously characterized and shown to be free of harmful genes. Several commentators inquired how the characterization was to be performed and the freedom from harmful genes demonstrated. Although the committee acknowledges that these terms are unavoidably vague, they do cite appropriate scientific methods to make relevant determinations. Again, this is a rapidly changing area and more clarity and precision can be expected with experience. Reduced containment requirements for this class of experiment are warranted because of the purified nature of clones. Further, the granting agency must approve the clone before containment conditions can be reduced, thus providing an additional element of review.

4. Another comment was related to the use of DNA from organelles (intracellular elements that contain special groups of genes for particular cell functions). Concern was expressed about the potential contamination of purified organelle DNA with DNA from viruses because of the similarity of their structures. The committee agrees, and the guidelines now specify a requirement, that the organelles be isolated prior to extracting DNA, as a further means of reducing the hazard of viral contamination.

5. Some commentators were troubled about the lowering of containment for that class of experiments involving recombinations with cell DNA segments purified by chemical or physical methods. They asked that procedures for determining the state of purification be more fully detailed and that the Recombinant Advisory Committee certify the purity. There are, however, appropriate techniques, such as gel electrophoresis, with which a purity of 99 percent by mass can be achieved and ascertained. There is no way for the committee to certify these results beyond repeating the experiments themselves. These techniques are well documented and described in the literature. I do not believe it is necessary or feasible for the committee to review each procedure for purification of DNA.

6. Comments were made concerning the use of DNA derived from animal viruses. It was urged that containment levels for this class of experiment be increased. On the basis of my review, I find the containment conditions appropriate to the potential hazard posed. As defined in the guidelines, experiments are to be done at very strict levels of containment and these can be lowered only when the cloned DNA recombinants have been shown to be free of possibly harmful genes by suitable biochemical and biological tests. This also pertains to DNA that is copied from RNA viruses. In no instance are the guidelines more lenient, and in most instances they are more stringent than conditions obtaining in many laboratories where such viruses are studied in non-DNA-recombinant experiments.

VI. CLASSIFICATION OF EXPERIMENTS USING CONTAINMENT SYSTEMS OTHER THAN E. COLI K-12

1. No issue with regard to these guidelines raised more comment than the use

of animal viruses as vectors. Of special concern to many commentators was the use of the simian (monkey) virus 40 (hereafter "SV40"). Some suggested a complete ban on the use of this virus; others urged its retention as a vector. SV40 is not known to produce any disease in man, although it can be grown in human cells and on very rare occasions has been isolated from humans. Many humans have received SV40 virus inadvertently in vaccines prepared from virus grown in monkey kidney-cell cultures. An intensive search has been made and is continuing for evidence that SV40 might cause cancer or be otherwise pathogenic for man. At present, it is my view that the extensive knowledge we have of SV40 virus provides us with sufficient sophistication to ensure its safe handling under the conditions developed for its use in the guidelines.

I believe work with SV40 should continue under the most careful conditions, but I do recognize and appreciate the concerns expressed over its possible harmful effects in humans. In light of these concerns, I asked the Recombinant Advisory Committee to review this section of the guidelines. The committee reconsidered the containment conditions for this class of experiments and judged them appropriate to meet the potential hazards.

This class of experiments will proceed under the most careful and stringent conditions. Work with SV40 virus will be done at the maximum level of physical containment (P4). The extraordinary precautions required in a P4 facility lessen the likelihood of a potential hazard from this work. Only defective SV40 virus will be used as vector; that is, the SV40 virus particles that carry the foreign DNA cannot multiply by themselves. When a number of strict conditions are met, this work will be permitted to go on at the third level of containment (P3), which in itself requires care and precision. It should be noted that SV40 virus and its DNA can be efficiently disinfected by Clorox and autoclaving. These are customary procedures for disinfecting glassware and other items used in SV40 animal-cell work.

Some commentators suggested that the containment criteria for experiments using polyoma virus as the vector be strengthened. There is no evidence that polyoma infects humans or replicates to any significant extent in human cells. It holds promise as a vector, as is more fully documented in an appendix to these guidelines.

2. Several commentators found the guidelines inadequate regarding experiments with plant host-vector systems. Because NIH shared these concerns, a group with extensive experience with plants was appointed to review this section. The group met concurrently with

* One member dissented from this position. During the discussion, additional language was recommended (and adopted) to ensure that the defective SV40-virus/helper-virus system, with its inserted non-SV40 DNA segment, does not replicate in human cells with significantly more efficiency than does SV40.

the Recombinant Advisory Committee in April 1976 and made several modifications. The suggested revisions were acceptable to the full committee, and we have included them in the guidelines.

The modifications are responsive to the stated concerns of the commentators. A description of greenhouse facilities is given, and physical containment conditions have been modified to take into account operations with whole plants. On the whole, the respective portions of the guidelines relating to plants are more fully explained and the intent is clarified.

I have also accepted the recommendation of the subcommittee to lower the biological containment level from EK2 to EK1 for experiments in which the DNA from plants is used in conjunction with the *E. coli* K-12 host-vector system, thereby setting containment in this instance at the same level required for experiments with lower-eukaryote DNA.

VII. ROLES AND RESPONSIBILITIES

1. Most commentators had suggestions for the section on the roles and responsibilities of investigators, their local institutions, and NIH. Commentators generally urged openness, candor, and public participation in the process, emphasizing shared responsibility and accountability from the local to the national level. We reviewed that section of the guidelines in light of these comments and have asked the Recombinant Advisory Committee to review certain issues.

It is clear that much of the success of the guidelines will lie in the wisdom with which they are implemented. Because of the importance of this section, especially in terms of safety programs and plans, we have carefully weighed the comments and suggestions made in this regard. NIH has a special responsibility to take a leading role in ensuring that safety programs are part of all recombinant DNA research. Dr. Barkley and a specially convened committee were asked to provide greater detail for safety, accident, and training plans for this section of the guidelines. Based on their recommendations, the section has been extensively rewritten to clarify the respective responsibilities of the principal investigator, the institution (including the institutional biohazards committee), the NIH initial review group (study section), the NIH Recombinant DNA Molecule Program Advisory Committee, and NIH staff.

This section has a definitive administrative framework for assuring that safety is an essential and integrated component of research involving recombinant DNA molecules. The guidelines require investigators to institute, monitor, and evaluate containment and safety practices and procedures. Before research is done, the investigator must have safety and accident plans in place and training exercises for the staff well under way.

Some commentators suggested that the investigator be required to obtain informed consent of laboratory personnel prior to their participation. Rather than rely explicitly on an informed consent document, the guidelines now make the

investigator responsible for advising his program and support staff as to the nature and assessment of the real and potential biohazards. He must explain and provide for any advised or requested precautionary medical policies, vaccinations, or serum collections. Further, an appendix to the guidelines includes detailed explanations for dealing with accidents, as well as instructions for the training of staff in safety and accident procedures.

In response to suggestions for epidemiological monitoring, the guidelines now require the principal investigator to report certain categories of accidents, in writing, to appropriate officials. NIH is investigating procedures for long-term surveillance of workers engaged in recombinant DNA research.

2. A number of comments on the role and responsibilities of the institutional biohazards committee were received. Comments were directed to the structure of the committee, the scope of its responsibility, and the methods for operation. Comments on structure included suggestions that the committee have a broadly based representation, especially in terms of health and safety expertise. Some others suggested NIH require certain classes of representation. In response to these suggestions, the guidelines now recommend membership from a diversity of disciplines relevant to recombinant DNA molecule technology, biological safety, and engineering.

For broader representation beyond the immediate scientific expertise, the guidelines now recommend that local committees should possess, or have available, the competence necessary to determine the acceptability of their findings in terms of applicable laws, regulations, standards of practice, community attitudes, and health and environmental considerations. The names of and relevant background information on the committee members will be reported to NIH.

In response to suggestions that decisions of the committee be made publicly available, the guidelines now recommend that minutes of the meetings should be kept and made available for public inspection.

Commentators generally approved of the responsibility given to the institutional biohazards committee to serve as a source of advice and reference to the investigator on scientific and safety questions. It was further suggested that the committee's responsibility be broadened in the development, monitoring, and evaluation of safety standards and procedures. In response to these suggestions, the guidelines now indicate that the institutional biohazards committee has the responsibility to certify, and recertify annually, to NIH that the facilities, procedures, practices, training, and expertise of involved personnel have been reviewed and approved. The Recombinant Advisory Committee suggested that examination might be unnecessary for P1 facilities, but we believe that all facilities should be reviewed to emphasize the importance of safety programs.

Some commentators suggested that the guidelines should stipulate that the local

committees be required to determine the containment conditions to be imposed for a given project (which the draft guidelines specifically noted was not their responsibility). The Recombinant Advisory Committee took exception to this suggestion. They urged NIH not to include these conditions as local requirements, arguing among other things that review by the NIH study sections would provide the necessary scrutiny at the national level and assure uniformity of standards in application of the guidelines. I do not believe that NIH should require the local institution to have its biohazards committee assess what containment conditions are required for a given project. On the other hand, the guidelines should not prohibit the local institution from having its biohazards committee perform this function. Accordingly, I have deleted the prohibition that appeared in the proposed guidelines.

Another suggestion was that the local committee ensure that research is carried out in accordance with standards and procedures under the Occupational Safety and Health Act (OSHA). This is an area of importance to the local institutions under Federal and State law, but need not be included as a requirement in the guidelines. NIH will maintain liaison with the Occupational Safety and Health Administration (Department of Labor) to ensure maximum Federal cooperation in this venture.

I would also encourage all institutions, as suggested by several commentators, to review their insurance compensation programs to determine whether their laboratory personnel, in the research area, are covered for injuries.

3. The commentators approved of having the NIH study sections responsible for making an independent evaluation of the classification of the proposed research under the guidelines, along with the customary judgment of the scientific merit of each grant application. This additional element of review will ensure careful attention to potential hazards in the research activity. The study sections will also scrutinize the proposed safeguards. Biological safety expertise shall be available to the study section for consultation and guidance in this regard.

4. Several commentators made suggestions concerning the structure, function, and scope of responsibility of the NIH Recombinant DNA Molecule Program Advisory Committee.

Comments on possible structural mechanisms for decision making included suggestions that there be a scientific and technical committee and a general advisory public policy committee. It was also suggested that the scientific committee include scientists who are not actively engaged in recombinant research, and that the public policy committee have a broad scientific and public representation.

I have carefully reviewed these comments and suggestions. In response, the following structure has been devised. The Recombinant Advisory Committee shall serve as the scientific and technical committee. Its membership shall continue to

include scientists who represent disciplines actively engaged in recombinant DNA research. In my view, it is most important that this committee have the necessary expertise to assure that the guidelines are of the highest scientific quality. The committee has provided this expertise in the past, and it must continue to do so. The committee shall also include members from other scientific disciplines.

It should be noted that the present committee recommended on its own initiative that a nonscientist be appointed. Emmette S. Redford, Ph.D., LL.D., Ashbel Smith Professor of Government and Public Affairs at the Lyndon B. Johnson School of Public Affairs, University of Texas at Austin, serves in that capacity. An ethicist has also been nominated for appointment.

The Advisory Committee to the Director, NIH, shall serve to provide the broader public policy perspectives. This committee, at its meeting on February 9-10, 1976, reviewed the proposed guidelines with the participation of public witnesses, and shall continue to provide such review for future activities of the Recombinant Advisory Committee.

In response to suggestions, the responsibilities of the Recombinant Advisory Committee have been expanded. In addition to reviewing the guidelines for possible modification as scientific evidence warrants, the committee will certify EK2 and EK3 systems. In response to requests by the investigator, local committee, or study section, the committee will also provide evaluation and review in order to advise on levels of required containment, on lowering of requirements when cloned recombinants are to be used, and on questions concerning potential biohazard and adequacy of containment provisions.

Commentators also asked that the committee review ongoing research initiated prior to the implementation of the guidelines. Now that the guidelines are being released, NIH-funded investigators in this field will be asked to give assurance, within a given period, that they will comply. Any investigators who constructed clones under the Asilomar guidelines will be asked to petition NIH for special consideration of their case, if the new guidelines require higher containment than did the Asilomar guidelines. Here the advice of the Recombinant Advisory Committee will be sought.

There were also suggestions that the committee certify chemical purification of recombinant DNA, but as I indicated earlier, these procedures are too well known to require NIH monitoring.

5. In light of comments received, NIH will provide review, through appropriate NIH offices, of data from institutional biohazards committees (including accident reports) and will ensure dissemination of these findings as appropriate. Dr. William Gartland will head the newly created NIH Office of Recombinant DNA Activities for these purposes. In addition, NIH will provide for rapid dissemination of information through its Nucleic Acid Recombinant Scientific

Memoranda (NARSM), distributed by the National Institute for Allergy and Infectious Diseases. NIH will also provide an appropriate mechanism for approving and certifying clones before containment conditions can be lowered.

With these extended modifications, the section of the guidelines dealing with roles and responsibilities now sets forth a more fully developed review structure involving the principal investigator, local biohazards committees, and the Recombinant Advisory Committee, as well as peer review committees. Guidelines now provide extensive opportunity for advice, from the local to the national level. Several levels of review and scrutiny are provided, ensuring the highest standards for scientific merit and conditions for safety.

The Recombinant Advisory Committee in conjunction with the Director's Advisory Committee shall continue to serve as an ongoing forum for examining progress in the technology and safety of recombinant DNA research. Their responsibility, and that of the NIH Director, is to ensure that the guidelines, through modification when called for, reflect the soundest scientific and safety evidence as it accrues in this area. Their task, in a sense, is just beginning.

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GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

JUNE 1976

- I. Introduction.
- II. Containment:
 - A. Standard practices and training.
 - B. Physical containment levels: P1 level (Minimal); P2 Level (Low); P3 Level (Moderate); P4 Level (High).
 - C. Shipment.
 - D. Biological containment levels.
- III. Experimental Guidelines:
 - A. Experiments that are not to be performed.
 - B. Containment guidelines for permissible experiments:
 1. Biological containment criteria using E. Coli K-12 host-vectors; EK1 host-vectors; EK2 host-vectors; EK3 host-vectors.
 2. Classification of experiments using the E. Coli K-12 containment systems:
 - (a) Shotgun experiments:
 - (i) Eukaryotic DNA recombinants;
 - (ii) Prokaryotic DNA recombinants;
 - (iii) Characterized clones of DNA recombinants derived from shotgun experiments.
 - (b) Purified cellular DNAs other than plasmids, bacteriophages, and other viruses.
 - (c) Plasmids, bacteriophages, and other viruses:
 - (i) Animal Viruses;
 - (ii) Plant Viruses;
 - (iii) Eukaryotic organelle DNAs;
 - (iv) Prokaryotic plasmid and phage DNAs.
 3. Experiments with other prokaryotic host-vectors.
 4. Experiments with eukaryotic host-vectors:
 - (a) Animal host-vector systems;
 - (b) Plant host-vector systems;
 - (c) Fungal or similar lower eukaryotic host-vector systems.
 - IV. Roles and Responsibilities:
 - A. Principal investigator;
 - B. Institution;
 - C. NIH Initial Review Group (Study Sections);

- D. NIH Recombinant DNA Molecule Program Advisory Committee;
- E. NIH Staff.
- V. Footnotes.
- VI. References.
- VII. Members of the Recombinant DNA Molecule Program Advisory Committee.

APPENDICES

- A. Statement on the use of *Bacillus subtilis* in recombinant molecule technology.
- B. Polyoma and SV40 Virus.
- C. Summary of Workshop on the Design and Testing of Safer Prokaryotic Vehicles and Bacterial Hosts for Research on Recombinant DNA Molecules.
- D. Supplementary Information on Physical Containment (Including Detailed Contents).

I. INTRODUCTION

The purpose of these guidelines is to recommend safeguards for research on recombinant DNA molecules to the National Institutes of Health and to other institutions that support such research. In this context we define recombinant DNAs as molecules that consist of different segments of DNA which have been joined together in cell-free systems, and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of the host's genome.

This is the first attempt to provide a detailed set of guidelines for use by study sections as well as practicing scientists for evaluating research on recombinant DNA molecules. We cannot hope to anticipate all possible lines of imaginative research that are possible with this powerful new methodology. Nevertheless, a considerable volume of written and verbal contributions from scientists in a variety of disciplines has been received. In many instances the views presented to us were contradictory. At present, the hazards may be guessed at, speculated about, or voted upon, but they cannot be known absolutely in the absence of firm experimental data—and, unfortunately, the needed data were, more often than not, unavailable. Our problem then has been to construct guidelines that allow the promise of the methodology to be realized while advocating the considerable caution that is demanded by what we and others view as potential hazards.

In designing these guidelines we have adopted the following principles, which are consistent with the general conclusions that were formulated at the International Conference on Recombinant DNA Molecules held at Asilomar Conference Center, Pacific Grove, California, in February 1975 (3): (i) There are certain experiments for which the assessed potential hazard is so serious that they are not to be attempted at the present time. (ii) The remainder can be undertaken at the present time provided that the experiment is justifiable on the basis that new knowledge or benefits to humankind will accrue that cannot readily be obtained by use of conventional methodology and that appropriate safeguards are incorporated into the design and execution of the experiment. In addition to an insistence on the practice of good microbiological techniques, these safeguards consist of providing both physical

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BETHESDA, MARYLAND
SEPTEMBER 9, 1976

MRS. DREW, DISTINGUISHED GUESTS, LADIES AND GENTLEMEN, TWO YEARS AGO DURING NIH OBSERVANCE OF BLACK HISTORY WEEK, MR. LOUIS PERKINS MADE THE RECOMMENDATION THAT WE HONOR CHARLES RICHARD DREW FOR HIS DISTINGUISHED AND PIONEERING WORK IN BLOOD RESEARCH. THIS MORNING'S CEREMONY IS THE RESULT OF THAT RECOMMENDATION.

IN 1940 WHEN THE "PLASMA FOR BRITAIN" PROJECT WAS INITIATED BY THE BLOOD TRANSFUSION ASSOCIATION, THE COLLECTION OF BLOOD AND PREPARATION OF THE PLASMA WAS UNDER THE SUPERVISION OF DR. CHARLES DREW. DR. DREW SERVED THEN AS SUPERVISOR OF THE BOARD OF MEDICAL CONTROL'S BLOOD PLASMA DIVISION.

IT'S INTERESTING TO NOTE THAT AT THAT TIME, SOME 36 YEARS AGO, DR. DEWITT STETTEN SENIOR SERVED AS CHAIRMAN OF THE BOARD. HIS SON, DR. DEWITT STETTEN, JR., NIH DEPUTY DIRECTOR FOR SCIENCE, IS IN OUR AUDIENCE TODAY.

UNTIL THE MID-1900'S, BLOOD WAS ADMINISTERED TO A PATIENT THROUGH "DIRECT" TRANSFUSION. A BLOOD VESSEL OF THE DONOR WAS CONNECTED TO A BLOOD VESSEL OF THE PATIENT. ADVANCES IN TECHNIQUE PROGRESSED FROM THESE BEGINNINGS IN THE EARLY 1900'S TO THE EVENTUAL DEVELOPMENT OF "INDIRECT" TRANSFUSION -- THE METHOD NOW IN USE. WITH INDIRECT TRANSFUSION CAME THE ADVENT OF BLOOD BANKING, UTILIZING TECHNIQUES OF COLLECTING AND STORING BLOOD FOR LATER USE.

DR. CHARLES DREW'S PIONEER WORK IN BLOOD BANKING, FOR THE PLASMA FOR BRITAIN PROGRAM, SERVED AS A FUNDAMENTAL GUIDE FOR SUBSEQUENT PRODUCTION OF BLOOD PLASMA AND LAID THE FOUNDATION FOR TODAY'S VAST BLOOD PROGRAM OF THE AMERICAN RED CROSS. BLOOD BANKING IS NOW AN INDISPENSIBLE MEDICAL RESOURCE. TODAY, AND EVERYDAY MORE THAN 18 THOUSAND PINTS OF BLOOD ARE TRANSFUSED IN THE UNITED STATES, OR APPROXIMATELY SEVEN MILLION PINTS A YEAR. AND WITH ADVANCES IN MEDICAL CARE, THE NEED FOR BLOOD HAS NEARLY TRIPLED IN THE LAST TEN YEARS.

AND QUITE NATURALLY, KNOWLEDGE ABOUT BLOOD IS IMPORTANT FOR ALL SCIENTISTS ENGAGED IN BIOMEDICAL RESEARCH. MY OWN INTEREST IN BLOOD RESEARCH BECAME MORE INTENSE WITH MY ASSOCIATION WITH NIH'S NATIONAL HEART INSTITUTE 15 YEARS AGO. I MIGHT POINT OUT, TOO, THAT DR. TED COOPER PRIOR TO HIS BECOMING THE ASSISTANT SECRETARY FOR HEALTH, HEW, WAS DIRECTOR OF THE NATIONAL HEART AND LUNG INSTITUTE, WITH MANY YEARS INTEREST AND WORK IN BLOOD RESEARCH.

WE ARE INDEED INDEBTED TO CHARLES DREW AND HIS PIONEERING WORK. BUT WHAT ABOUT THIS PHYSICIAN, THIS MAN, A FATHER, HUSBAND, SURGEON, SCIENTIST, TEACHER AND ATHLETE? MUCH HAS BEEN WRITTEN ABOUT HIM. MUCH COULD BE SAID ABOUT HIM. POSSIBLY, DURING THE SHORT TIME WE HAVE HERE THIS MORNING, A CITATION HE RECEIVED COULD SERVE TO SUMMARIZE A DEDICATED CAREER THAT WAS ALL TOO BRIEF. I QUOTE FROM THE CITATION FOR THE AWARD OF THE DEGREE, DOCTOR OF SCIENCE, MADE TO DR. DREW BY AMHERST COLLEGE, ON JUNE 15, 1947:

"GRADUATE OF AMHERST IN THE CLASS OF 1926. OUTSTANDING ATHLETE OF THE DECADE OF THE 1920'S; WINNER OF PRIZES, HONORS, TROPHIES, AND AWARDS WITHOUT NUMBER AT AMHERST AND MCGILL. ROCKEFELLER FOUNDATION FELLOW IN SURGERY. BRILLIANT INVESTIGATOR OF THE PROBLEM OF BLOOD AND PLASMA PRESERVATION: YOU WERE CHOSEN UNANIMOUSLY DIRECTOR OF THE PLASMA PROJECT FOR GREAT BRITAIN IN THE DARK MONTHS WHICH FOLLOWED DUNKIRK. DIRECTOR OF THE FIRST AMERICAN RED CROSS PLASMA BANK. ASSISTANT DIRECTOR OF BLOOD PROCUREMENT FOR THE NATIONAL RESEARCH COUNCIL. WINNER OF THE SPINGARN MEDAL. AUTHOR OF FOURTEEN LEARNED BOOKS AND ARTICLES. NOW PROFESSOR AND HEAD OF THE DEPARTMENT OF SURGERY AT HOWARD UNIVERSITY AND CHIEF SURGEON AND MEDICAL OFFICER OF FREEDMAN'S HOSPITAL. YOUR GENIUS AND YOUR DEVOTION HAVE SAVED THE LIVES OF TENS OF THOUSANDS."

YOUR APPEARANCE HERE TODAY, IN THIS AUDITORIUM AND THOSE OF YOU WHO ARE WATCHING ON THE 14TH FLOOR BY CLOSED CIRCUIT TELEVISION, IS SPLENDID TESTIMONY OF YOUR FEELING FOR CHARLES RICHARD DREW, AS WE DO HIM HONOR WITH THE UNVEILING OF HIS PORTRAIT.

IT IS WITH A GREAT DEAL OF PLEASURE THAT I WELCOME EACH OF YOU TO THE NATIONAL INSTITUTES OF HEALTH AND TO THIS CEREMONY.

AT THIS TIME I SHOULD LIKE TO INTRODUCE THE ASSISTANT SECRETARY FOR HUMAN DEVELOPMENT, HEW — THE HONORABLE STANLEY THOMAS, JR.

MRS. DREW, ON BEHALF OF THE NATIONAL INSTITUTES OF HEALTH AND THE CITIZENS OF THIS COUNTRY, I SHOULD LIKE TO PRESENT TO YOU A FRAMED COLOR PHOTOGRAPH OF THIS PORTRAIT OF YOUR HUSBAND.

WHILE THIS IS A SMALL TOKEN, IN PRESENTING IT TO YOU WE SIGNIFY THE ESSENTIAL ROLE THAT YOU, AS HIS LIFE-LONG PARTNER, AND YOUR FAMILY PLAYED IN MAKING POSSIBLE THE CONTRIBUTIONS OF CHARLES RICHARD DREW IN THE INTEREST OF ALL MANKIND.

REMARKS BY DONALD S. FREDRICKSON, M.D.
DIRECTOR, NATIONAL INSTITUTES OF HEALTH

for

INTRODUCTION OF HEW SECRETARY DAVID MATHEWS
IN CONNECTION WITH BANQUET OF
"RESEARCH AND THE PRACTICE OF MEDICINE IN 1976"

SHERATON HALL, SHERATON PARK HOTEL
WASHINGTON, D.C.
THURSDAY, SEPTEMBER 16, 1976

DR. ROSE, DISTINGUISHED COLLEAGUES, LADIES AND GENTLEMEN. THE MOST COMPLEX JOB IN WASHINGTON--THE MOST DEMANDING, THE MOST EXASPERATING, IS NOT AS YOU MAY THINK--THE CHAIRMAN OF THE TEA TASTER'S PANEL OF THE FDA, NOR THAT OF OFFENSIVE COACH OF THE REDSKINS. IT IS THE POSITION HELD BY OUR SPEAKER THIS EVENING.

BORN IN GROVE HILL, ALABAMA, HE WAS PHI BETA KAPPA AT THE UNIVERSITY OF ALABAMA. HE RECEIVED HIS DOCTORATE IN THE HISTORY OF AMERICAN EDUCATION FROM COLUMBIA UNIVERSITY. (AND I THINK THE PERSPECTIVES OF AN HISTORIAN MAY BE INVALUABLE FOR REMAINING NORMOTENSIVE IN THE CAPITOL TODAY.

A FORMER INFANTRY OFFICER AT FORT BENNING, GEORGIA, HE WAS VOTED ONE OF THE TEN OUTSTANDING YOUNG ME IN AMERICA IN 1969.

IN THAT SAME YEAR, AT THE AGE OF 33, HE BECAME THE YOUNGEST PERSON EVER TO BE PRESIDENT OF THE UNIVERSITY OF ALABAMA. ON LEAVE FROM THAT INSTITUTION, HE BECAME A MEMBER OF THE PRESIDENT'S CABINET LAST YEAR. HE WAS ACCOMPANIED TO WASHINGTON BY HIS CHARMING WIFE, MARY, AND THEIR EQUALLY LOVELY DAUGHTERS, (LEE ANNE) AND LUCY.

IN HIS OFFICIAL CAPACITY AT HEW, HE HAS HAD THE DIFFICULT TASK OF PROVIDING "EQUAL TIME" FOR EACH OF THREE SECTORS OF RESPONSIBILITY--HEALTH, EDUCATION, AND WELFARE.

THE NATIONAL INSTITUTES OF HEALTH, AS PART OF THE PUBLIC HEALTH SERVICE, HAS APPRECIATED HIS CONCERN AND SUPPORT.

IT IS WITH GREAT PLEASURE THAT I PRESENT TO YOU THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE--DR. DAVID MATHEWS.

OVERSIGHT HEARING ON IMPLEMENTATION OF NIH
GUIDELINES GOVERNING RECOMBINANT DNA RESEARCH

JOINT HEARING
BEFORE THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON
LABOR AND PUBLIC WELFARE
AND THE
SUBCOMMITTEE ON
ADMINISTRATIVE PRACTICE AND PROCEDURE
OF THE
COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE
NINETY-FOURTH CONGRESS
SECOND SESSION
ON
EXAMINATION OF NIH GUIDELINES GOVERNING
RECOMBINANT DNA RESEARCH

SEPTEMBER 22, 1976



Printed for the use of the Committee on Labor and Public Welfare
and the Committee on the Judiciary

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FOR RELEASE UPON DELIVERY



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20814

STATEMENT BY

DR. DONALD S. FREDRICKSON, DIRECTOR

NATIONAL INSTITUTES OF HEALTH

ON RECOMBINANT DNA RESEARCH

BEFORE THE

SUBCOMMITTEE ON HEALTH

SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE

SEPTEMBER 22, 1976

Mr. Chairman and Members of the Subcommittee:

It is a pleasure to appear before you today to discuss the NIH guidelines on recombinant DNA research.

In June, the National Institutes of Health, with the approval of the Secretary of HEW and the Assistant Secretary for Health, issued guidelines to govern NIH-supported research on recombinant DNA molecules. Accompanying the guidelines was a document describing in detail the issues which the Director of NIH considered in reaching the decision to release the guidelines. These guidelines, governing research conducted at the laboratories of NIH as well as projects supported by grants and contracts, delineate stringent safeguards for the conduct of experiments involving the production of recombinant DNA molecules and their insertion into organisms such as bacteria. The object of the guidelines is to minimize the risks associated with recombinant DNA research--primarily through a series of procedures aimed at physical and biological containment of possibly dangerous organisms--while permitting research of great potential benefit to mankind. The NIH guidelines replaced the recommendations from the 1975 Asilomar Conference on Recombinant DNA Molecules, which permitted research under less strict conditions.

Recombinant DNA molecules are formed in the laboratory from recombination of segments of deoxyribonucleic acid, the material that determines the hereditary characteristics of all living cells. These techniques, permitting genetic information from quite different organisms to be combined, have a remarkable potential for furthering the understanding of fundamental biochemical processes of both lower and higher organisms.

Recombinant DNA research has strong potential in medicine as well as in science and technology generally. In medicine it is capable of providing hitherto unobtainable knowledge of the organization and expression of genes in health and disease. It possibly may also permit economical production of important medicinals. Potential benefits in agriculture and industry include more abundant crops and synthesis of industrially important biochemical agents such as enzymes.

There are risks, however, as well as potential benefits in the new research. For example, bacteria with transplanted genes may prove hazardous to man or other forms of life. Like many of the potential benefits, these risks remain speculative, for there is still scanty evidence that genes from one form of life can be expressed in any other form. We must assume, however, that they may be. Thus our present state of knowledge dictates strict controls on this form of experimentation.

The NIH guidelines prohibit certain types of experiments--those, for instance, that might produce disease germs with increased resistance to antibiotics. Other experiments will go forward under special safety conditions. The guidelines have a definitive administrative framework for assuring that safety is an essential and integrated component of research involving recombinant DNA molecules. The section dealing with roles and responsibilities sets forth a developed review structure involving the principal investigator, local biohazards committees, and the NIH Advisory Committee, as well as peer review committees. The guidelines now provide extensive opportunity for advice, from the local to the national level. Several levels of review and scrutiny are

provided, ensuring the highest standards for scientific merit and conditions for safety. We believe these provisions will afford protection, and with a wide margin of safety, to workers and the environment while permitting this type of research to proceed. And the NIH is sponsoring additional experimental work to determine possible hazards and new safety practices and procedures.

Development of the Guidelines

Recombinant DNA research brings to the fore certain problems in assessing the potential impact of basic science on society as a whole, including the manner of providing public participation in those assessments. The field of research involved is at the leading edge of biological science. New information is accruing rapidly and requires continuing evaluation and re-synthesis. The experiments involved are extremely technical and complex. Molecular biologists active in this research require diligence to keep abreast of the newest developments. It is not surprising that scientists in other fields and the general public have difficulty in understanding advances in recombinant DNA research. Yet public awareness and understanding of this line of investigation is vital.

It was the scientists engaged in recombinant DNA research who called for a moratorium on certain kinds of experiments in order to assess the risks and devise appropriate guidelines. At their behest, the National Academy of Sciences created a committee that organized an international conference at Asilomar Conference Center in California, held February 1975. The committee also called on the NIH to establish

an advisory committee to draft guidelines for the conduct of this research. At Asilomar, temporary guidelines were issued pending issuance of NIH guidelines.

In response, the NIH Recombinant Advisory Committee (formally "NIH Recombinant DNA Molecule Program Advisory Committee") was established in October 1974 to advise the Secretary of HEW, the Assistant Secretary for Health, and the Director of NIH to accomplish these tasks. The several meetings at which the Recombinant Advisory Committee developed its proposed guidelines in 1975 were announced in the Federal Register and were open to the public. The committee, after working several draft versions, reached agreement on a recommended revised version of proposed guidelines that were referred to the NIH Director for review in January 1976.

A special meeting of the Advisory Committee to the Director, NIH, was convened in February of this year to review these proposed guidelines. In addition to current members of the committee, a number of former committee members as well as other scientific and public representatives were invited to participate in the special February session. There was ample opportunity for comment and an airing of the issues, not only by the committee members but by public witnesses as well. All major points of view were broadly represented.

The proposed guidelines were reviewed in the light of the comments and suggestions made by the participants at the public hearing as well as extensive written correspondence received after the meeting. The NIH has published a volume containing the transcript of the public hearing of the Director's Advisory Committee, all correspondence directed

to the NIH on this matter, and summaries of meetings with representatives from Government, Departments, and Agencies, Congressional staff, and industry. The Decision of the Director, NIH, that accompanied the release of the guidelines in June is based on that record.

Steps are underway for further opportunity for debate, scrutiny, and subsequent decisions relevant to the guidelines. The guidelines were published in the Federal Register on July 7, and a 120 days' period was allowed for comment. Further, in response to the recommendations of public commentators, the NIH undertook an environmental impact assessment in accordance with the National Environmental Policy Act of 1969. A draft environmental impact statement was published in the Federal Register on Thursday, September 9, 1976, for public comment. The statement was given widespread distribution to interested environmental Federal, State, and local groups for comment. In this way, yet another review will be provided from the perspective of the environmental impact of this research.

Application to Public and Private Sector

The Department and NIH have given high priority to the implementation of the NIH guidelines and their application beyond the NIH. A meeting was held with representatives of relevant HEW agencies and other departments of the Federal Government on April 8. The purpose was to exchange information on recombinant DNA research and to discuss the applicability of NIH guidelines to research or regulatory activities of other departments and agencies.

A meeting was also held on June 2 with representatives of private industry to provide them with full information about the guidelines and to help determine the present and future interest of industrial laboratories in this type of research. The meeting afforded one of the first opportunities for industry representatives to convene for discussion of this research.

The expressed concern for the extension of these guidelines to other Federal agencies and the private sector is shared by the NIH and the Department of Health, Education, and Welfare. The letter from you, Mr. Chairman, and Senator Javits to the President expressed well these timely concerns. Following the NIH initiatives, the Department has been reviewing an appropriate mechanism to allow for a policy review of Government activities in this research area, including relevant activities in the private sector. The Department has proposed to the President that an interagency committee be created to review the activities of all Government agencies conducting or supporting recombinant DNA research or having regulatory authority relevant to this scientific field. This committee could also coordinate activities with the private sector. The President has written to relevant Department Secretaries and Agency Heads urging their cooperation and participation in naming representatives to serve on this committee.

The interagency committee will assist in facilitating compliance with a uniform set of guidelines for the public and private sectors and provide coordination among the several Government agencies that support or conduct this research. It is mandated to suggest appropriate administrative or legislative proposals deemed appropriate for national

implementation. For this purpose a review of authorities--the Public Health Service Act, the Occupational Safety and Health Act, the National Environmental Policy Act, and other relevant statutes--will be carried out.

It should be noted that the National Science Board has adopted by resolution the NIH guidelines for all such research supported by the National Science Foundation. We anticipate similar letters of endorsement from all of the Federal agencies that are now conducting or supporting such research, or consider that they may do so in the near future.

Since the NIH meeting with private industry in June and following publication of the NIH guidelines in the Federal Register, the Pharmaceutical Manufacturers Association has been reviewing the applicability of the guidelines to industry research activities. The PMA has expressed general support for the guidelines with relatively minor revisions considered necessary to meet the needs of industry.

In order to ensure that implementation of the guidelines within the NIH be achieved without delay, an NIH Office of Recombinant DNA Activities was created in June to administer and coordinate activities. This office will serve as liaison to the institutional biohazard committees for administration of the guidelines. There will be special emphasis on activities pertaining to the operation and implementation of containment and safety practices and procedures. The NIH office will also closely monitor reports and information concerning accidents, containment, and safety research innovation.

To ensure that those who conduct recombinant DNA research will have notice and adhere to the guidelines, the NIH distributed the guidelines to approximately 25,000 grantees and contractors. The investigators and institutions supported by the NIH have a special responsibility for maintaining the safety practices outlined in the guidelines, and the NIH will work closely with them to fulfill that objective.

In response to public concern that broad support for the guidelines be solicited, the NIH undertook to distribute them through a number of channels. Letters were sent to professional organizations soliciting support for the guidelines among their member scientists and to editors of journals requesting editorial endorsement. The guidelines were also sent to all science attaches of foreign embassies located in Washington and to U.S. science attaches in our embassies in foreign countries. Various international health and scientific organizations have also been briefed on the guidelines.

The NIH recognizes its responsibility to continuing discussions on the international level to ensure that there be as uniform a standard of guidelines as possible to govern the conduct of this research in all nations. As an example of international cooperation, the European Molecular Biology Organization recently announced plans for a voluntary registry of recombinant DNA research in Europe. Following this EMBO initiative, NIH shall similarly maintain a voluntary registry of investigators and institutions engaged in such research in the United States. Plans for establishing this registry are under way, and the new interagency committee will be asked to address the scope of the registry as one of its earliest tasks. Great Britain has endorsed continuation of

recombinant DNA research, and a Government report has just been issued containing guidelines that technically are similar to the NIH guidelines.

Patent Policy Review

Currently there is also a review underway of the Department patent policies as they relate to discoveries in recombinant DNA research. A number of universities where such research is being conducted are reviewing possible patent applications for these discoveries. Stanford University and the University of California have filed patent claims in this research area and have solicited the views of the Department and the NIH. These patent activities, the certitude that other important inventions in this field are forthcoming, and the public's apprehension over control of recombinant DNA research compel inquiry into whether the Department's policies for allocating invention rights are consonant with the concerns about this research.

Invention rights are normally allocated in either of two ways under current Department patent regulations:

The Department has institutional patent agreements with 65 universities having identified technology transfer capabilities. Such an agreement provides the institution the first option to ownership in all inventions made in performance of Department research, subject to a number of conditions deemed necessary to protect the public interest. Stanford and the University of California are among the institutions that hold such agreements with the Department.

Second, for those institutions who do not have an institutional patent agreement, the Department defers determination of ownership until an invention has been made. Under the deferred determination policy, an innovating institution may petition the Department for ownership of an invention after it is identified. In the past, approximately 90 percent of all such petitions have been granted.

The Department's policy of allocating invention rights is designed to facilitate the transfer of technology from the bench to the marketplace by inducing industrial investment and continued development of inventions generated with Department support. The incentives provided by Department patent policy have encouraged the development of new technology in general and afforded patent protection for some inventions to the economic benefit of the United States. The control of DNA research envisioned by the guidelines, however, requires a delicate balance between need for rapid exchange of information and a potential means for achieving greater uniformity in safety practices by setting conditions for safety in licenses under patent agreements.

Stanford and the University of California have indicated a willingness to consider modification of their patent agreement with the Department as it relates to such research. A number of possible policies, short of the present allocation of rights under the agreement, are currently being considered by the NIH as possible alternatives to the present allocation of rights made under all such agreements. As part of that review, the NIH has solicited the views not only of members of the NIH

community but of the public as well, including all those who participated in the public hearing on the guidelines.

The prudence and caution inherent in the guidelines must also be reflected in patent policies underlying administration of recombinant DNA research inventions.

Conclusion

In summary, the potential benefits and risks of recombinant DNA research have posed a singular challenge. The prospects of harnessing these techniques to the benefit of man are indeed great. From what we know today, we must assume that if these promises are to be realized, our efforts must be marked by extraordinary diligence to avoid harm. This combination of benefits and risks provides not only opportunity but obligation for the scientific community and the public to proceed together in assessment of risks and benefits and to agree upon procedures that will allow the continuation of these investigations under conditions of minimal risk.

Our immediate task is threefold: First, to maintain a satisfactory process for updating and revising the guidelines in the light of both public scrutiny and new research developments. Secondly, to pursue steps to ensure that all sectors of the scientific enterprise in this country concur and adopt these or comparable guidelines, and to use all influence available to us to encourage a consistent policy throughout the world. Thirdly, we must now, in concert with all interested parties, consider whether additional measures to assure a common approach to problems here are advisable. Let me assure the Committee that the

Department will make every effort to accomplish these tasks.

Thank you for the opportunity to discuss these issues before the Committee. My colleagues and I would be happy to try to answer questions you or other members may have.

Recombinant Odyssey

An Account of the Status of Regulation
of Recombinant DNA Research in Western
Europe, from a visit made by the Director,
NIH, September 23 to October 2, 1976.

Donald S. Fredrickson, M.D.

Recombinant DNA Activities

World Health Organization (WHO)

As derived principally from discussion in Geneva with Dr. K. Bögel, who is the principal staff officer for this matter, the WHO has in process the following activities related to recombinant DNA.

First, there is a recommendation of a subcommittee of the Advisory Committee on Medical Research (ACMR) about recombinant DNA research. This committee, including Drs. de Duve (Belgium-US), Nossal (Australia), Lederberg (USA), Fauve (France), Solov'ev (USSR) and Lord Zuckerman (United Kingdom), has concluded that WHO has a global responsibility in this field and should coordinate information and disseminate it to member states. No attempt is being made to develop guidelines (cf. a forthcoming document ACMR 7/18/76).

As discussed at a meeting (supported by WHO and NIH) on September 14-17 in Geneva and attended by Drs. Gartland, Wanner, and Oviatt of NIH, WHO intends to take two further actions. First, it will bring a scientist from Pisa to Geneva for a few weeks, with the assignment to review and compare the NIH, U.K., and possibly the Canadian guidelines. Second, it will convene four working safety groups who will address these problems: (1) safety of laboratory equipment, (2) international transfer of research materials, (3) emergency services, and (4) maximum containment facilities (P4)--all in relationship to broad problems of microbiological research. Attempts will be made to set standards.

Bögel has also been urged by the ACMR to develop plans for a plenary session, largely of representatives from international committees of U.N. agencies--such as the Division of Human Rights, the International Labor Organization, etc., for "discussions of the benefits and hazards of recombinant DNA research." The ACMR has pushed such a proposal and he intends to present the idea to Director General Mahler. I have given Dr. Bögel my impression of the hazards and benefits of a forum dedicated primarily to offering scientists an opportunity to give their personal views on such research. In line with some comments also made to the National Academy of Sciences (US) Forum Committee on a similar meeting planned in Washington next March, it is my view that WHO should concentrate on an analysis of events since Asilomar and on the international role for WHO in this and similar problems. There is potential disaster in a WHO public discussion of this topic if it lacks adequate structure and balance. I urged Drs. Bögel and Goodman to suggest to Dr. Mahler that we discuss this proposal, if it becomes a serious one. I will also urge our NIH representatives to any of these working groups to press for care in planning such a public session.

Overall, WHO does have a unique role to play in internationalization of recombinant DNA research issues because it is one of very few organizations which includes all of the countries likely to become involved. WHO attempts

to develop international standards of laboratory safety have a potential for good. As NIH pursues its standard-setting in this area, we must also consider involvement of other nationals and attempt to keep WHO informed of what we are doing or contemplating. Joint sponsorship by WHO and NIH of certain conferences may be useful. A special consideration is the stringency of NIH definitions of containment levels. Some scientists, for example, are concerned, and possibly misunderstand, that the airflow requirements for hoods in our P3 and P4 specifications exceed the local commercial capacity to meet such requirements. Dr. Theo Staehelin of Basel will visit Emmett Barkley in several weeks to elaborate on this problem. Any potential inability of other nationals to meet NIH guideline specifications could limit their applicability abroad.

Switzerland

My impressions of recombinant research issues in this country were derived mainly from a 3-hour meeting with a group of Swiss scientists convened in the Biozentrum of the University of Basel. This group consisted of (1) Prof. Werner Arber, Department of Microbiology, Biozentrum, Klingelbergstrasse 70, CH 4056, Basel; (2) Theo Staehelin, Basel Institute for Immunology (B.I.I.); (3) Charles Steinberg, B.I.I.; (4) Susumu Tonegawa, B.I.I.; (5) Masahiro Sugiura, B.I.I.; (6) Walter Wehrli, Plasma Division, CIBA-GEIGY, Basel; and (7) Christoph Moroni, Friedrich Miescher Institute, Postfach 273, CH 4002, Basel. Most influential among these was Prof. Arber, who is Chairman of the Swiss National Commission for Experimental Genetics, which will be the focus for development of whatever guidelines become effective in Switzerland. (More on this later.)

Recombinant research is proceeding in some academic laboratories in Switzerland. The Swiss scientists judge that it is not taking place in industry as yet. Control of the Swiss pharmaceutical industry is largely concentrated in the hands of chemists and classical pharmacologists. They and their boards of stockholders are extremely conservative, and until biologists move up into the directorate (or unless the profits of recombinant work become more obvious), the major companies here are judged unlikely to invest in this research. Roche, which underwrites an independent Basel Institute of Immunology, will shortly have, for the first time, a cell biology unit in its company laboratories. Theo Staehelin will head it, and the first P3 unit will be constructed at the research unit across from the main plant. There is at present no P4 facility in Switzerland, according to Arber.

Questions about genetic manipulation have twice been raised politically in Switzerland. The first instance, three years ago, was a question posed in the Bundesrat by Oehen, head of the Republican Party. His party and the comparable National Action Party constitute only about 5 percent of the Swiss electorate, but periodically contribute a disproportionate share of excitement from the radical right. (For example, it was Schwarzenbach, head of the National Action Party, who several years ago proposed to remove all foreign workers from Switzerland, a suggestion that aroused intense debate before it

fell in a national referendum.) When Oehen spoke against "genetic engineering" in the Bundesrat, scientists rallied quickly to help the government compose an answer and the matter died without publicity. A year later, in the Bundesrat of Kanton Zurich, the work on α -beta mutations by Weissman in the Zurische Technische Hochschule was questioned. The matter died after some discussion in both newspapers and on T.V. At about this time a symposium on genetic recombination was held in Davos, which was attended by Paul Berg. The Swiss Society of Molecular and Cell Biology became involved and there ensued a lively scientific and philosophical discussion.

Industry next became concerned and convened a meeting in Basel between both industrial and academic scientists. The scientists decided to organize to deal with the problem and preferably connect its efforts to the Swiss Academy of Medical Science, the Academy of Natural Sciences, or the Government. The scientists decided to use the first of these because of the medical connotations of the subject. The Academy of Medical Science has 50 rotating members chosen from both academic and practicing physicians and dentists. It meets once yearly and has more prestige than reputation for social action.

Thus, a year ago a National Commission for Experimental Genetics was formed, with Arber as President. The intent of the commission to study the safety of recombinant DNA work was announced, with minimal attention in the press. The other 10 members include scientists, physicians, microbiologists, the Director of the Swiss NIH (not to be confused with its American cousin, since Federal support of Swiss biomedical research comes through the Swiss National Foundation), and the government office for science and research. No philosophers, ethicists, or other laity have yet been included.

In November 1976, the Commission meets again to discuss the NIH, U.K. guidelines and any recommendations of EMBO (European Molecular Biology Organization) or ESF (European Science Foundation) that may precede the meeting. The Swiss are active in EMBO (Weissman from Zurich is the representative), ESF, and ICSU (International Council of Scientific Unions). Arber believes the Swiss will probably not attempt to devise separate national guidelines. (There is a general feeling here that EMBO will recommend the U.K. guidelines for its members.) My question to the group about who, then, would form the GMAG (Genetic Manipulation Advisory Group) provided for in the U.K. rules to supply ad hoc decisions about experiments met with a general reaction that workers in separate European countries were unlikely to submit their protocols to Heidelberg (or London or Brussels?) for individual rulings. This consideration, plus the absence of supranational enforcement provisions, leads me to wonder if implementation will not have to fall along national lines.

As for extension or enforcement, the Swiss believe a current "law on epidemics" could provide a statutory base for extension and enforcement of a Commission recommendation. They are considering registration and modes of exchange of information. There are two interesting attitudes about Swiss industry that apply to this problem. One is a general belief that industry is so conservative that it will welcome strict controls over this research as a matter of

protecting itself from liability. The other is an impression that Swiss patent law forces unusual secrecy ("if two outsiders know of a process, it is automatically in the public domain"). If this last is true, it leaves much uncertainty that an open community of research can be created.

The support for research here is both National (total biomedical support about 100 million in francs per year), Kantonal, and private (mainly industrial). Thus no single funding source can control research practices by (economic) sanctions. Like us, the Swiss scientists wonder who will control the maverick entrepreneurs who "open a plant in Libya" for manufacture outside any guidelines. Rejection of a marketable recombinant product—economic control on an international scale—was mentioned as a last resort. Inspections and police actions impress no one here as effective controls. They, too, view peer pressure as a key regulator and are in favor of journal policies requiring discussion of containment used in experiments.

There is considerable concern in Switzerland about how scientists can keep up with the NIH actions, particularly of the Recombinant DNA Committee. The Nucleic Acid Recombinant Scientific Memoranda (NARSM) is generally regarded as inadequate. We must consider how to augment this organ so that it might become an "International Gazette of Recombinant News." The actions of our Recombinant Committee have now become of great significance to a world-wide community. That community includes many key scientists, like Arber, who perforce will shape national actions in many different countries. They need to receive all of our publications relative to this subject without undue delay.

European Science Foundation

This is an infant association, founded in 1975, headquartered in Strasbourg. Its Secretary-General is Dr. F. Schneider, until last year Secretary-General of the Max Planck Gesellschaft and who still works part time at the Gesellschaft offices in Munich (Residenzstrasse 14). I met with Dr. Schneider in Munich early in the morning of September 27.

As in all of the offices and labs which I have visited on this trip, there is a much-thumbed xerox copy of the NIH guidelines and decision paper of June 23. Dr. Schneider was fully aware and very laudatory of the efforts we have made during this past summer, the praise perhaps was partly intended to soften what he had to say about imminent ESF actions. In 1975, an ESF Working Group on Genetic Manipulation was established. Its membership is attached (see "C" in the ESF booklet, page 33). The chairman is a medical person from Denmark, Prof. P. Riis. There is a variety of other disciplines represented on the committee, and a member from each member-country of ESF.

In a report of September 10 of this group (handed out at the EMRC meeting on October 1), they have recommended ESF adoption of the U.K. report with formation of a working committee consisting of a member from each "national DNA recombinant advisory group," plus, Dr. Schneider hopes, a representative

of the NIH DNA Advisory Committee. Dr. Schneider cites the following reasons for adopting the U.K. report: (1) the NIH report is viewed as a little less strict on physical containment, and the ESF group is a little skeptical about biological containment (he noted specifically that the U.K. P3 was tougher than NIH P3); and (2) the NIH guidelines "are intended only to govern governmental research," while the U.K. report emphasizes the participation of "public health officers" for enforcement throughout Britain. He also feels that by some combined European agreement which is "tough on containment," the number of participating labs could be restricted and work would thus proceed slowly and carefully. The matter of enforcement across national lines, of course, still remains unsolved.

I emphasized to Dr. Schneider that the attempt to form a unified European-U.K. approach to guidelines could only be considered highly desirable. I acquainted him with the recent developments toward extension of NIH guidelines to the entire U.S. scene and of forthcoming, and slightly different, Canadian guidelines. Also I posed the question of how the U.K. principle of ad hoc decisions on each experiment would be approached for all Europe. Finally, I did promise NIH representation on the ESF committee envisioned if this plan becomes operative. I also hoped proscribed research and prohibitions of release of recombinant products at present would be considered in any general agreement. Dr. Schneider indicated this would probably be included.

ESF plans must be adopted by the Executive Council and Assembly. Actions may occur in November. (See discussions of the EMR Council heads in Helsinki below.) EMBO is independent of ESF and its actions will weigh upon the degree of acceptance of any ESF proposal.

Dr. Schneider is one of the opinion-makers who should receive all of the NIH material on our guidelines. We promised to keep in close touch.

Germany

Munich: On September 27 I met with a small group having an informal conference on recombinant DNA in the Virusabteilung of Lynen's Max Planck Institut für Biochemie in Munich, a Division headed by Dr. Peter Hans Hofschneider. People from several Institutes, including the Krebsforschungsinstitut in Heidelberg, and industry were present. Here, I found that, contrary to the information just obtained from the general secretary at the Max Planck Gesellschaft, the active molecular geneticists in Germany were about to embrace the NIH guidelines.

A committee, consisting of molecular biologists, and organized by the Deutschen Forschungsgemeinschaft, has more or less come to the conclusion that the NIH guidelines should be adopted in Germany. Dr. Joachim Messing at the Institut für Biochemie has been spending his evenings and time off for the past several weeks translating the guidelines into German. (He will send us a copy.) They are not aware of the ESF or EMBO leanings toward the

U.K. version, and cannot envision a single European ad hoc committee. They find our guidelines clear and reasonable, and have been much interested in the decision paper accompanying them. They know, as did the Swiss, all about "the Sinsheimer position," also those of Chargaff and Beckwith, and all about Cambridge. The German position expressed here is gratitude for the NIH work; and, since we have done it, they see no virtue in attempting to write their own guidelines. They do believe it may be difficult to have a suitable biohazards committee for each institution, endorse a policy of containment discussions in any research publications, and believe that guidelines are preferable to law in realistic control of such research.

In Germany, there are 13 or 14 active recombinant labs, none yet known in industry. The scientists at this meeting were not knowledgeable about legal aspects of extension of any rules to industry. They believe industry to be very conservative and not a threat to violation of guidelines. There is no P4 in Germany, except that being constructed in Heidelberg (EMBO).

Dr. Gerhard Sauer (Krebsforschungsinstitut) and Dr. Hofschneider know two Russians in this field--Ilya Georgev and V. M. Zhdanov in Moscow--and believe they should be useful contacts. Zhdanov is at the D. I. Ivanovsky Institute of Virology, Moscow, and Georgev is at an Academy of Sciences Institute for Microbiology, Budapest, Hungary. He knows all the Russian as well as Hungarian workers.

I visited the site of a (first) proposed P3 lab at the Max Planck Institut here. The Germans here believe it is now time to make the guidelines work and not the moment for another international Asilomar. There has been little public discussion of recombinant work in Germany, no Der Spiegel articles, etc. Today's Munich papers discuss Dr. Hofschneider's lecture (public) on the subject, given this week. The clipping (attached) mentions the NIH guidelines. I am impressed here as elsewhere on this visit with the competence, sobriety, and rational attitude on the part of the scientists engaged in this work. I was introduced to a German biology class at the Institut, busy doing experiments with reverse transcriptase. The students had no questions on guidelines (or the Ford-Carter debates).

In Cologne, I visited at the University with Prof. Peter Starlinger and Dr. Dorfler. Both are molecular biologists and, again, very familiar with the NIH and U.K. guidelines. They conveyed much the same impression that I got at Munich, a preference for the NIH guidelines for Germany. One additional reason that surfaced was the feeling that since they often publish in U.S. journals, they might have to use our guidelines. I dismissed this as not relevant, and that NIH had no proprietary rights on guidelines, provided others used were comparable in substance. The most important point gained from this discussion was the fundamental inability of the German universities to accept the institutional role we assign in the United States. The structure of German universities is basically that of a collection of faculty, pursuing their own interests, while providing the obligatory teaching functions with a minimum of administrative cohesion. The chancellor, usually

a lawyer, is essentially an administrative officer. The deans are rotating professors, who have neither the time in office, the power, or the interest in creating a structure fostering interdisciplinary coordination or oversight. Hence there is a minimum of "hybrid" professors with entree to more than one department, a perhaps excessive autonomy of department chairmen, some rigidity of curriculum, and little or no experience with institutional review boards for such activities as clinical research or special problems in laboratory safety.

Some influence for uniform curriculum and departmental structure is provided by the German Science Council (Deutsches Wissenschaftsrat) which makes recommendations that influence the support, both Federal and Länder, provided the universities. The other major force comes from the Deutschen Forschungsgemeinschaft (DFG) which provides most of the research grants. It is this organization which must lead the academic community in following any special guidelines for research practices. The DFG has formed a Senatskommission für Sicherheitsfragen bei der Neukombination von Genen. Its membership includes Breuer of Bonn (Chairman), Eggers of Köln, Goebel of Würzburg, Hofschneider of Munich, Starlinger of Köln, and Zachau of Munich. Permanent ministerial "guests" are Binder, BMFT (research); von Bulow, BMJ (justice); Schumacher, BMJFG (health); Schwick, Behring-Werke Marbury, and Frau Dr. Zarnitz of Stiftung VW Hannover. Its chairman, Prof. Breuer, is a medically trained clinical chemist and Vice President of the DFG. Note the membership from the German Research and Technology, Justice, and Health ministries as well as from Volkswagen Foundation. The representation from industry (Behringwerke) is there because of his scientific expertise, not because of his industrial linkages. I have talked to Breuer, Hofschneider, Starlinger, and Binder from this commission. Again, the questions of how to avoid legislation and of what existing statutes to invoke for regulation are not yet solved in Germany.

DFG: The conversation with Dr. Breuer held on September 29 at the headquarters of the DFG was very useful--and scientist-to-scientist in orientation. He agreed with Starlinger about the problems that IRB's posed for the universities, but noted that such bodies will have to be formed for purposes of review of clinical investigation; so the move is under way for structures to deal with other guidelines as well. The German scientists are very suspicious of IRB's as devices for impeding clinical research; we discussed how they are formed and operate in the United States and my own belief that they have improved the quality of U.S. clinical investigations.

The DFG will have the dominant role in recombinant guidelines in Germany. It is clear that here there is a preference for NIH guidelines, skepticism about an ESF role, and a preference for proceeding along national lines within a broader community of agreement on safety practices. Asked of what role I thought ESF might play, I saw a European Recombinant Committee, with national representation, linked to the NIH (or American - or North American) Recombinant Advisory Committee, allowing use of either NIH or U.K. guidelines nationally, with a European registry tied to the American one. There will

clearly be pressure brought on major European journals to request containment descriptions in DNA research reports. There will also need to be means of providing certain EK2 hosts or vectors on an international basis—a responsibility which NIH needs to consider its initiative. Finally, I indicated that if Germany adopted NIH guidelines, we would urge it to maintain liaison representation at the NIH Recombinant DNA Committee.

France

Under the DGRST (Direction Generale Recherche Scientifique et Technologic) there are two French Committees particularly concerned with recombinant DNA. These include an Ethical Review Group and a Technical Committee; the latter is all scientist in composition. It presently reviews all applications to the government for such experimentation, which effectively means control over all recombinant experiments thus far underway in France. No applications above P2, or from industry, have yet been considered. The committee is currently proceeding under the Asilomar or "last NIH draft." It may continue under an amalgam of NIH-U.K. rules until some pattern is set.

One P4 facility exists at the Pasteur Institut, another underway at the Institute of Molecular Biology at Ku University in Paris. The French hope to use the EMBO facilities in Heidelberg as well. There are yet no existing laws in France which will permit ready extension of guidelines to the private sector.

EMRC Meeting (Helsinki)

The EMRC is now a "standing committee" of the ESF. Its meeting on October 1 involved an agenda of many items, most principally the DNA question, ethics, and medical research and, at the insistence of the Finnish hosts, the Helsinki Declaration. The last got nowhere and the second not far from the starting line. The DNA question was a charged one. The British were extremely polite but were not, I think, eager to lose the initiative of the ESF Committee to adopt U.K. guidelines for Europe. I was eager to clear up some (ESF) misconceptions about NIH guidelines but determined to hold national pride in check sufficiently to prevent a War of Roses over two similar guidelines "which, after all, were both progeny of the international agreement at Asilomar." The main thing is to get a system that works in Europe, conforming to the important principles we all agree upon. Miss Coates of the ESF Secretariat was somewhat apologetic about the ESF Committee recommendations (attached). She reviewed the dynamics of the Committee in a detailed way and provided me with a copy of a Health and Safety recommendations from Britain (attached) which had upset all concerned in both Britain and the ESF. (Inspection of this document shows it to be comparable to OSHA suddenly appearing with too sweeping a definition of recombinant research and demanding that all proposals be sent to it straightaway).

The EMRC did not finish its meeting by accepting the U.K. guidelines. (The Williams report and the ESF committee recommendations were handed out at the table.) Let the sketchy recall of that portion of the meeting speak for itself.

DISCUSSION ON DNA IN EMRC MEETINGS

Belgium: EMRC should take a position on this essentially medical problem, even though the ESF has taken the initiative.

Britain: It seems that the ESF Commission has the matter well in hand. Copies of the Riis (ESF) Committee report (attached) and the Williams Committee Report have been circulated before lunch.

ESF Secretariat: (reviewing history) . . . the ESF was first asked to look into this at the suggestion of the Swedish Research Council in 1974. It was requested to consider the state of Europe's position in the scientific, social, and economic aspects of the matter The ESF Committee first suggested mandatory (national) registration of all such experiments and an examination of the relevant national laws to govern it The Committee also suggested that the forthcoming NIH guidelines would be used for Europe and urged close European cooperation These suggestions were circulated in March and favorably received The Committee met again in May 1976; it did not yet have the U.S. guidelines; National Commissions to consider actions had been created by Switzerland, the Netherlands, France, Sweden, and the U.K., and Germany and Ireland were to soon have them. Meanwhile, the Committee heard that the U.K. guidelines would be available shortly In September 1976 the Committee met again and now had the NIH and U.K. guidelines for comparison. (Britain and EMBO's representation particularly were anxious to have the U.K. guidelines adopted). . . . "In some ways the U.K. proposal seemed a little closer to what the ESF Committee had earlier proposed, viz., a higher emphasis on physical containment, a central committee to review all activity, a stricter P-3 perhaps meant somewhat fewer experiments" There was concern about mixing two sets of guidelines . . . to stress close collaboration with NIH

Netherlands: Have been taking measures for over a year . . . a single committee, appointed by the Minister of Science Policy, sees all proposals . . . follow NIH guidelines at present "with discussions perhaps evolving toward Williams Report" . . . the legalities of implementation are difficult.

Belgium: What about Dutch government and industry, since matter is of national concern, not only academic? EMRC again urged to form its own committee on the subject.

Switzerland: Opposes EMRC group to "advise" ESF.

Germany: States Germany is adopting the NIH guidelines . . . opposes a separate EMRC committee.

Denmark: Agrees on last point.

U.K.: Says ESF should take lead since agriculture also concerned, thus not merely a medical affair . . . note Director of NIH is here and he suggests he comment on the U.S. scene.

NIH: Thanks U.K. for opportunity to clarify current state of affairs in the U.S., viz., extension to rest of government, PMA acceptance of guidelines . . . formation of interagency governmental committee . . . likely applicable regulatory power such as OSHA . . . the similarities overwhelming the differences between the NIH and U.K. sets of guidelines . . . the great importance of liaison between all concerned.

Meeting concludes with agreement that all EMRC members will get copy of NIH guidelines and consider what to do at next meeting. Sixty copies will also go immediately to all ESF members.

The important aspect of this meeting was the briefing on where the U.S. has progressed in its use of guidelines, permitting the EMRC to make as informed a choice as possible. This will likely come too late, however. It is clear that the parent ESF (allied with EMBO) will try to make a decision "for Europe"; still, it is likely the individual countries will have the last say.

Finnish Finale

In Finland there seems to be little or no recombinant DNA research at present. On the evening of October 1, U.S. Ambassador Austad gave a dinner for us. The other guests were 16 leading Finnish scientists--representing nuclear physics, mathematics, chemistry, philosophy, genetics, anatomy, medicine, etc. After dinner, the Ambassador (who used to do this for Channel 5 as "Mark Evans" several years ago) assembled everyone in a great circle and moderated the conversation to a single subject with his accustomed command of panels and studio audiences. The topic was the "New (Synthetic) Biology." The discussion was intense; perhaps because of 800 miles of common border with Russia and six months of night, the Finns have a justifiable penchant for melancholia. One scientist was intensely pessimistic of any control of a "dangerous science." One, a professor of nuclear medicine, asked for a recounting of the "municipal events in Boston (Cambridge)." (It seems no scientist has not heard of the moratorium imposed on Harvard.) The Rector

of the University opined that you can never engage the public in scientific decision-making. The nuclear physicists, who had, in a way, been through this before, seemed more optimistic than the rest. The philosopher said nothing. There was a touch of Ibsen, perhaps a little of Beckett, in the scene. Comparing events in the Old World with the New, one concludes it is fortunate that the dissidence has thus far been loudest where native optimism is stronger. Europe is not yet prepared for the likes of Jonathan King and Soloman Garb.

COMBINED FEDERAL CAMPAIGN RALLY AT NIH -- Building One
Wilson Hall
October 13, 1976
10:00 A.M.

DR. FREDRICKSON'S REMARKS:

First, I want to thank all of you here for attending this morning.

As CFC Chairman for NIH, I have asked Dr. Donald Tower, Director of the National Institute of Neurological and Communicative Disorders and Stroke, to assist me as Vice-Chairman. The responsibility for conducting the campaign belongs to Dr. Tower and his staff. Even more important, perhaps, are all those keypersons who make the employee contacts and who are really the key to a successful campaign.

This year we are emphasizing full participation by all employees, consistent with our campaign theme, "More People Giving, and People Giving More." Participation has gone down over the past three years at NIH. Though we exceeded our dollar goal last year, only 60 percent of NIH personnel contributed. Let all of us do our best to raise that level of participation.

Let me touch briefly on some of the specific features of this year's campaign.

First, the Prince George's County Community Fund situation has been resolved and those voluntary agencies are

now members of the United Way of the National Capital Area. This means there will not be a separate Prince George's Community Fund campaign this year.

The United Black Fund is also included among the United Way agencies. More than 30 agencies are committed to service under the United Black Fund.

Also, for the first time, contributors wishing to designate contributions to the campaigns conducted in nine Mid-Maryland counties may do so. In the past only contributions to those voluntary services listed with CFC of the National Capital Area could be accepted.

The CFC benefits three major charities. Two-thirds of the funds go to the United Way's 145 local health and welfare agencies, including those of the United Black Fund. Almost 16 percent goes to the 11 National Health Agencies, and a little over six percent is allotted to six International Service Agencies. Administrative costs, including printing materials, accounting services and the like, were only three and one-half percent of the total collected last year.

Last year's quota was \$199,400. Final figures showed that NIH contributed \$204,326, or 103 percent of the original goal.

Last year, 18 NIH units contributed to the campaign, and 12 either reached or topped their goals of 100 percent.

The goal for NIH's 11,000 employees this year is \$234,194. Our campaign has been underway only slightly over one week, and the latest figures show that an amount of \$33,405 has been contributed. This is 14 percent of our goal. Contributors number 937, or nine percent of the goal, and the average gift is \$35.65.

We are pleased with the dollar generosity but we are naturally concerned about the low percentage of contributors. We can and should do better.

We all need to be reminded of the deeply human story of the people who benefit from CFC. And people are what this campaign is all about.

We still have more than two weeks to go in our drive to go over the top again. If all of you here maintain your momentum, your interest and enthusiasm, I am confident that we will not only exceed our quota again, but we will get more people involved in giving and increase our participation.

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TESTIMONY OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BEFORE
 THE COMMISSION ON EXECUTIVE, LEGISLATIVE AND JUDICIAL SALARIES
 ON TUESDAY, NOVEMBER 9, 1976

I am pleased to have this opportunity to testify before the Commission about the problems that the National Institutes of Health are experiencing as a result of existing salary limitations. On October 22nd I submitted to Mr. Liebttag a written statement describing the effects of a noncompetitive salary structure on our recruitment and retention of senior scientific staff. Today, I would like to highlight the key points made in that statement and answer any questions you may have about our situation.

Let me begin by emphasizing that NIH is an integral part of a large biomedical research community which consists primarily of universities and medical schools. Movement of staff between the various institutions within this community is essential to the maintenance of creativity in each of its components. While in-breeding may be dangerous to the health of any organization, it is fatal to an organization whose function is research.

In recent years the movement of experienced scientific staff between NIH and other research institutions has increasingly become a one-way flow - out of NIH. Now, when a key staff member accepts a better offer in academia, it is always difficult and frequently impossible to attract outside candidates with comparable experience and stature. The major factor contributing to this trend is the difference between the salaries and benefits provided by academic institutions and those available under the Civil Service system. To give you a conservative estimate of the competition that we face, I will quote some median salary figures from the Association of American Medical Colleges Annual Salary Survey for Fiscal Year 1975-76. During a period when the top salary

- additional income: consultations, honoraria, fees, royalties
- tuition
- favorable retirement

for Civil Service employees was \$37,800, half of the strict full-time* professors of clinical sciences received at least \$45,000 in salary and half of the strict full-time clinical science department chairmen received at least \$57,000 in salary. Individuals who were in the top 20 percent of the range for clinical science faculty - the group from which NIH is generally trying to recruit - made at least \$55,000 as full professors and \$68,000 as department chairmen during this same 1975-76 period. Since benefits in academic institutions are generally superior to those in Civil Service, a total income comparison would show an even greater advantage for our competitors.

Salary competition is not new to NIH, but the problems we are facing as a result of it are much more critical than in the past. It is no longer just a question of individual, highly specialized positions that are difficult to fill. The cumulative effect of not providing adequate salaries over the last several years has dangerously eroded our capacity to retain staff who earlier committed themselves to a career with us. It has so significantly increased the economic sacrifice that senior academic faculty would have to make that a substantial number are unwilling to even talk about the possibility of working for NIH. I find myself in a very uncomfortable position when I approach individuals whom I would like to attract to leadership positions. Generally, I am asking them to accept more responsibility at a lower salary with no prospect for improvement in the foreseeable future.

The long range solution to our problems lies in the development of a total compensation system which would make us more competitive with both the salary and benefits of academic institutions.

* According to AAMC survey definitions, strict full-time medical school faculty are those who receive their entire professional income as a fixed annual amount from funds controlled by the medical school or its parent institution, who devote their full time to the programs of the medical school, and whose professional activities are under the direct auspices of the medical school.

For the immediate future, our principal goal is to prevent further deterioration of our staffing situation. The approach we are recommending as an interim solution is to cut the linkage between the Executive Pay Schedule and Section 208(g) of the Public Health Service Act - the Public Health Service's statutory authority for filling scientific and professional positions requiring specially qualified personnel.

From NIH's point of view, there are three advantages to this approach:

- First of all, raising the salary ceiling on Section 208(g) positions is targeted toward that portion of our senior staff where the need has been clearly demonstrated. Over the years we have used appointments under this authority to give recognition to our most talented scientists and professionals, and these are the individuals whom we can least afford to lose. At the same time, it is our best mechanism for bringing in experienced staff from other research institutions, since it is exempt from some of the time-consuming requirements applicable to supergrade positions.
- Secondly, the Section 208(g) authority would give us the greatest flexibility in pay setting, since it provides a salary range rather than grades and steps. The salary compression of recent years has made it impossible for us to make distinctions in pay based on differences in responsibilities at the top levels. We would use the 208(g) salary range to reestablish such distinctions at NIH.
- Finally, approaching the salary problem through Section 208(g) would take advantage of PHS's long experience with this authority. The basic provisions of Section 208(g) were added to the Public Health Service Act on August 15, 1950; subsequent amendments have increased the number of positions to 150 for the entire Public Health Service, of which NIH has almost 100.

I have a detailed legislative history of Section 208(g) which I will leave with you.

What we need as a permanent solution is a system that would permit the Director of NIH to relate the salary and benefits of scientific staff to the salary and benefits provided to their counterparts in universities and medical schools. There is legislative precedent for such a system in the Uniformed Services Health Professions Act of 1972, which provides that "civilian members of the faculty and staff shall be employed under salary schedules and granted retirement and other related benefits prescribed by the Secretary of Defense so as to place the employees of the (uniformed services) university on a comparable basis with the employees of fully accredited schools of the health professions within the vicinity of the District of Columbia." I have already asked my staff to begin work on the details of a proposal for legislation to meet NIH's particular needs.

If there are any questions, I would be happy to answer them now.

"COSMIC THOUGHTS"*

Donald S. Fredrickson, M.D.**

This conference has been called to discuss a number of issues which have arisen in recent years concerning immunization. The history of immunization and its public health achievements extends back to the origins of the Republic. Two hundred years ago, Washington was skeptical about the use of the new practice of smallpox vaccination to protect soldiers of the Continental Army; but Jefferson was quick to recognize the potential advantage of this new approach, even though the virus was then unknown and the method far more risky than that of today.

Now the immense value of immunization in the prevention of diseases is a matter of record. Yet on this 200th Anniversary of our country we continue to face controversy regarding it. Such problems are neither new, nor a matter of despair. Over the centuries infectious diseases have been the concern, as they are today, of parliaments, juries, commissions, and panels. To quote Sir McFarland Burnett: "Infectious disease is and always has been part of the every day experience of life and in every generation, men of affairs have had to cope the best they could with the practical problems it presents; while priests, philosophers, and, later, scientists have had perhaps the harder task of determining the significance of such disease in accordance with the intellectual outlook of their time."

*Presented at the Conference on Immunization, National Institutes of Health, November 12, 1976

**Director, National Institutes of Health

We have just passed through what Loren Eisley has termed "Darwin's century." It might also have been called "Pasteur's century." About one hundred years ago the recognition of microbes as the cause of illness heralded a whole new approach for treatment and prevention. In some instances, public health measures were sufficient to control epidemics. For example, cholera epidemics abated when sewage was separated from drinking water. Other illnesses, such as diphtheria and tetanus, also fell before new methods of immunization. But all achievements were not made in the distant past. In the fifties we saw the success of immunization against polio and in the sixties against measles and rubella which resulted in the reduction of the various complications of these diseases.

And yet these dramatic and highly effective immunization programs have had counter effects which are to be reflected in some of the issues raised at this conference. Success leads to complacency. No one advocates a policy of continuing immunization if the danger is eradicated. Save for smallpox, such total success is rarely achieved. If immunization against common pathogens does not continue, an unimmunized and virgin public is always potentially susceptible to epidemics.

Successful immunization programs also give rise to a popular but erroneous notion that all infectious diseases are no longer important matters of public health. This view is reinforced by the effective use of antibiotics in the treatment of bacterial infections.

Frequently the public, and sometimes members of our profession, lose sight of a fundamental difference between immunization and antibiotic therapy. Immunization not only prevents illness; it also prevents spread of infection to susceptible contacts. It is control measured in terms of populations. Antibiotic treatment is often only effective for a single patient. The treated patient has almost always spread his illness to susceptible contacts prior to antibiotic therapy.

There are other problems, some created by the remaining expectations that soar higher with each success. Manipulation of the immune systems of the millions without some compromises is a formidable challenge. Enormous credit is due to science, industry, and the health system alike for the present record of safety in suppressing epidemics. But all vaccines are not perfect and vigilance can never be relaxed. The chances of human errors, the tendency of antigens to commit genetic heresy, the growing legal complications to testing and development, the huge investments in mass campaigns . . . these and other things place great responsibilities upon us to guide wisely a public dependent upon our trusteeship of its health.

Furthermore, we seem always to be on some frontier, far from complete mastery of infectious diseases. Influenza and pneumonia, together, are still the fifth more common cause of mortality. Care of infectious diseases continues to consume a major portion of a doctor's time. One out of four visits to doctors' offices is in search of treatment for an infection. A portion of these illnesses could be prevented if immunization programs we

now have were more broadly promoted throughout our society. For many, however, the etiologic agents--viral and bacterial--have yet to be identified. Only the easy and obvious solutions have been found for those diseases most susceptible to control. There is as yet no vaccine and no antimicrobial compound even for many others with known etiologies.

With so much at stake, now is the time to capitalize on the heritage of "Pasteur's century." A revolution in medical thinking has yet to be fully exploited for the prevention of disease. The basic principles are sound, but they must be infused with the incisive language of molecular and cell biology and the new immunology. Research and development must bring to health care new opportunities for diagnosis and for intervention in the prevention and treatment of infection. In addition, we must constantly reassess the adequacy or, indeed, the need for current practices. This will require a new commitment to studies on etiology and prevalence of infectious diseases and on the impact of vaccines on the costs of health.

This is also the time to capitalize on current suspicion that certain chronic diseases may have infectious origins. Some of these may be direct processes, or mediated through immunological mechanisms. In this regard, I need do no more than recall the research of NIH's Dr. Carleton Gajdusek, Nobel Laureate in Physiology and Medicine for 1976, which began as a study of a peculiar mental illness in a cannibalistic tribe in New Guinea and led to the discovery of a new class of viral agents which result in a degenerative process of the brain.

Finally, we can not disregard recent evolutionary events among bacteria which will influence our future plans for immunization, perhaps extending the search for vaccines to other common pathogens. I refer here not to genetic engineering by man, but to the recombinations between bacterial species which obey neither NIH guidelines nor Cambridge City Council moratoriums. From these recombinations have recently emerged new antibiotic resistance among certain bacteria. During the last two years we have seen the occurrence of penicillin resistant strains of Hemophilus influenzae and Neisseria gonorrhoeae. This is perplexing, because this type of penicillin resistance did not occur in the prior thirty years that penicillin had been widely used. Despite our cautious optimism it now appears that these two pathogenic bacteria may have acquired plasmids from our own E. coli which carry the genetic information for beta lactamase or penicillinase production.

At the close of "Darwin's century" it is ironic that we have seized control of man's evolution; perhaps in recombinant DNA research we shall capture far greater territory. Still, Nature has infinite devices which we cannot yet control, even when we understand them. William McNeill has a nice title for our subject: *Plagues and Peoples*. This meeting is a time for taking stock on where we stand in this endless struggle. Let us be harsh with ourselves, but hopeful.

NIH welcomes you warmly to this conference. Where Federal demeanor forbids us to offer spirits, we shall not stint in access to our spiritual reserves. And the coffee shall flow throughout the day in the cafeteria, a minute away on the floor below.

INTRODUCTORY REMARKS FOR

NIH LECTURE

DR. PAUL BERG

NOVEMBER 17, 1976

LADIES AND GENTLEMEN:-

IT IS INDEED A PLEASURE FOR ME TO WELCOME YOU THIS EVENING, AND TO INTRODUCE TO YOU OUR EMINENT LECTURER, DR. PAUL BERG.

DR. BERG IS WILLSON PROFESSOR OF BIOCHEMISTRY AND THE FORMER CHAIRMAN OF THE DEPARTMENT OF BIOCHEMISTRY AT STANFORD UNIVERSITY SCHOOL OF MEDICINE.

I MUST ACKNOWLEDGE FIRST, AND WITH DEEP GRATITUDE, THE ROLE THAT PROFESSOR BERG HAS PLAYED RECENTLY IN CHAIRING THE COMMITTEE ON RECOMBINANT DNA MOLECULES OF THE ASSEMBLY OF LIFE SCIENCES, NATIONAL RESEARCH COUNCIL - NATIONAL ACADEMY OF SCIENCES.

THE DELIBERATIONS OF THAT COMMITTEE WERE, AND STILL ARE OF INESTIMABLE VALUE TO THE NATIONAL INSTITUTES OF HEALTH AND TO ME PERSONALLY, AS WE HAVE SOUGHT, AND CONTINUE TO SEEK, WITH GREAT CARE, TO BE THOROUGHLY RESPONSIVE TO ALL OF THE PUBLIC AND SCIENTIFIC CONCERNS SURROUNDING THE CONDUCT OF RECOMBINANT DNA EXPERIMENTS.

DR. BERG IS AN ALUMNUS OF PENNSYLVANIA STATE UNIVERSITY AND WAS AWARDED THE PHD DEGREE IN BIOCHEMISTRY BY WESTERN RESERVE UNIVERSITY IN 1952. FOR TWO YEARS HE WAS A POSTDOCTORAL RESEARCH FELLOW AT THE INSTITUTE OF CYTOPHYSIOLOGY IN COPENHAGEN AND AT WASHINGTON UNIVERSITY IN ST. LOUIS. HE REMAINED AT WASHINGTON UNIVERSITY AS A SCHOLAR IN CANCER RESEARCH AND AS A FACULTY MEMBER UNTIL MOVING TO STANFORD IN 1959.

DR. BERG'S STUDIES ON THE GENETIC APPARATUS THAT DIRECTS THE SYNTHESIS OF PROTEINS EARNED HIM THE ELI LILLY AWARD IN

(MORE)

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BIOCHEMISTRY IN 1959 AND THE CALIFORNIA SCIENTIST OF THE YEAR AWARD FOR 1963.

IN 1966, AT THE AGE OF 40, DR. BERG WAS ELECTED TO MEMBERSHIP IN THE NATIONAL ACADEMY OF SCIENCES AND THE AMERICAN ACADEMY OF ARTS AND SCIENCES AND MORE RECENTLY HAS BEEN ELECTED TO THE INSTITUTE OF MEDICINE. HE IS THE IMMEDIATE PAST-PRESIDENT OF THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS AND IS A MEMBER OF THE AMERICAN SOCIETY OF MICROBIOLOGISTS AND A NON-RESIDENT FELLOW OF THE SALK INSTITUTE FOR BIOLOGICAL STUDIES.

DR. BERG TWICE HAS RECEIVED THE HENRY J. KAISER AWARD FOR EXCELLENCE IN TEACHING, IN 1969 AND 1972. IN 1972 HE WAS DESIGNATED BOTH THE HARVEY LECTURER AND THE V.D. MATTIA LECTURER.

IN THE LABORATORY, HIS EARLY STUDIES WERE CONCERNED WITH PROTEIN SYNTHESIS, AND PARTICULARLY THE ELUCIDATION OF THE MECHANISMS OF AMINO ACID ACTIVATION PRIOR TO THE SYNTHESIS OF THE PEPTIDE BOND. IN THESE STUDIES DR. BERG SHOWED THAT THE INITIAL STEPS IN PROTEIN SYNTHESIS INVOLVE SPECIFIC ACTIVATING ENZYMES AND SPECIFIC ADAPTORS, THE T-RNAs, FOR EACH OF THE AMINO ACIDS. THESE STUDIES CONTRIBUTED TO OUR UNDERSTANDING OF THE ESSENTIALLY ERROR-FREE ASSEMBLY OF AMINO ACIDS INTO PROTEINS.

MORE RECENTLY, HE HAS FOCUSED HIS ATTENTION ON THE MECHANISM OF GENE EXPRESSION IN HIGHER ORGANISMS, AND THE INTERPLAY OF VIRAL AND CELLULAR GENES IN THE REGULATION OF GROWTH AND DIVISION. IN THE COURSE OF THESE STUDIES DR. BERG AND HIS COLLEAGUES HAVE PIONEERED THE DEVELOPMENT OF NEW ENZYMATIC AND PHYSICAL APPROACHES

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TO THE ANALYSIS OF THE STRUCTURE OF SIMPLE VIRAL GENES, THEREBY MAKING POSSIBLE A MOLECULAR APPROACH TO GENETICS.

THESE BASIC APPROACHES ARE AIMED ULTIMATELY TOWARD THE FURTHER DEVELOPMENT OF KNOWLEDGE CRUCIAL TO THE PREVENTION, MANAGEMENT AND POSSIBLY THE CURE OF HEREDITARY DISEASE.

DR. BERG WILL SPEAK TO US THIS EVENING ABOUT THE TUMOR VIRUS, SV40, ABOUT WHICH A NUMBER OF PREVIOUS NIH LECTURES HAVE BEEN PRESENTED. HIS TITLE IS "DISSECTIONS AND RECONSTRUCTION OF THE SV40 GENOME."

DR. BERG.

ACCEPTANCE OF SHANNON BUST FOR NIH

by

Donald S. Fredrickson, M.D.

The real history of any period in the life of an institution is a summation of the attitudes and accomplishments of the people who were then joined in its name and purposes. When we think of the National Institutes of Health in the years between the opening of the Clinical Center (1953) and the late sixties, it is easy, natural, indeed inevitable, to cast that epoch in personal terms. It was, to everyone, the "Shannon Era."

In his Discourses, Machiavelli said, "He errs least and will be most favored by fortune, who suits his proceedings to the times and always follows the impulses of his nature." In just this way did James Shannon lead this institution in its period of unprecedented growth and formation as an extraordinary enterprise for the benefit of mankind. How richly he merited and how well he acquitted himself in that position of leadership.

In accepting this likeness of Dr. Shannon for the National Institutes of Health, I am quite aware that it is not only symbolic of him, but of certain of his qualities, which we have long accepted as the standards for this unique community: a certain toughness and durability, a look forward, a kindness but unremitting insistence on excellence . . . the proper blend of skepticism and of optimism.

For the NIH of the present I gratefully acknowledge the heritage he has bestowed upon us. And for the NIH of the future, I accept this splendid and indelible reminder of the man.

Presented at 4:00 p.m. in Wilson Hall, Building 1, National Institutes of Health, on November 23, 1976.

The public governance of science

Donald S. Fredrickson

A quarter of a century ago, there was little that one could call "public governance" of science. There were no formal arrangements for setting a social priority to the scientific question one hoped to answer. The proprieties were largely covered by the Hippocratic oath and, except for rules on the use of radioactive isotopes, there were few regulations. Nor, it should be said, was there much in the way of public patronage of science. Allocation of federal revenues for salaries, assistants, and instruments, and for offsetting other costs of research in academic institutions, was limited mainly to contracts begun in war-time.

A transition came rather suddenly as the enterprise acquired an enduring commitment from the state. Increasingly generous annual investments were made to expand laboratories and to train participants. Since 1950, the nation's pool of doctoral scientists trained for biomedical research has risen sixfold—from an estimated 15,000 to 90,000.¹ The principal beneficiaries were, and still are, the academic medical centers and parts of their universities complementary to the purposes of this support. The purposes were simple. Information was to be discovered that could be transformed into better health and longer life for the investors and their children.

The National Institutes of Health, assigned to sponsor the operation, became an almost unique example of government patronage and power to influence science. For nearly thirty-five years it has fostered self-governance by a profession that, because of the technical nature of the work, has borne responsibility for distributing public resources to itself. Performance of this trust has been uncompromising in its insistence on excellence and sound stewardship. And there is ample and continuing witness of an abundant return on the investment.

Nevertheless, the past several years have been replete with signs—

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Dr. Fredrickson delivered the address reproduced here as a Columbia University Bicentennial Lecture, December 9, 1976.

statements, editorials, actions—indicating that the relations between biomedical science and its public trustees are changing significantly, if not seriously decaying and in need of restoration. We are now in a major transitional phase. Under concerned public scrutiny, biomedical research is passing from an extended period of relative privacy and autonomy toward an engagement with new ethical, legal, and social imperatives. We move fitfully toward greater public governance of science. For the sake of the public good, it is vital that we find the proper limits to this shift.

We do not have time here to trace the history of three centuries of relations between scientists and the rest of society, although much philosophical instruction might be found there. We should be aware that societies are prone to cyclical reactions to various privileged institutions. And we should note that disillusionment with science has often attended renewed recognition that the scientific method cannot be extended to all human problems. An excess of scientism, as in the nineteenth-century flourishes of Marxian dialectic, can also be disillusioning. So today can lack of primary medical care in the inner city.

Modern science has not inherited the kingdom foreseeable in the scientific optimism of the *Discourse on Method*² or *The New Atlantis*.³ But neither Descartes nor Bacon could have anticipated the degree to which science would become an anxious dependent on society's limited reserves. Nor could they have known how many of science's triumphs would bear overtones to trouble the patron's mind.

Most uneasiness with the method derives from its products. The science and the technology tend to be confused, and dissatisfaction with the latter leads to ambivalence about the former. This situation cannot be evaded. As Jacques Monod puts it: "Modern societies, woven together by science, living from its products, have become as dependent on it as an addict on his drug." Monod, in *Chance and Necessity*, is expressing his impatience with the animists who "owe their material wherewithal" to science while rejecting its fundamental ethic—that the "systematic confronting of logic and experience is the sole source of real knowledge."⁴ This thesis provides a tonic to brace modern science for confrontation with its critics, for there are invaluable elements of the scientific method that cannot be sacrificed to uncomprehending "reform." This is not to say, however, that the best defense of the rationalist position is reiteration of essential doctrine. Rather, the resolution must be sought in deliberate, sensitive accommodation between objective knowledge and value judgments.

In this broader context, let us consider the nature of biomedical

research. This is an activity throughout biology, in which the tools of multiple disciplines are applied to increase knowledge of living systems and to resynthesize that knowledge to useful generalities. It is intensely reductionistic, yet humane, for its purpose is extension of those generalities to particulars that may improve the human condition. This involves "application" or "development," along with assurance of the safety and efficacy of the products. The process must go farther for realization of purpose: successful application requires diffusion to the consumer, and his acceptance. The value of any part of this sequence tends to be judged on the effectiveness of the whole.

For emphasis we restate this proposition as it pertains to the natural scientist who needs state support for his role in the continuum. The beauty of a discovery, such as the universality of the genetic code, is not lost on the layman; but his appreciation is proportionate to the real or expected effect of the discovery on himself. If the effect is not immediate, the layman may accept a promissory note, for he and his forebears have learned to be patient with the potential of processes they do not fully understand. But continued patronage depends upon continuing expectation.

Today it is widely perceived that health care may be overly oriented toward technology, and, not necessarily as a result, that health care is also too costly. Where both of these perceptions can be laid to faulty participation by science in the assessment and transfer of technology, science may be taxed with cooperation in reducing the faults. While there is disagreement with my position, I believe these necessary contributions include an effort to improve the now informal process of arriving at consensus on what new knowledge should be extended to health-care practice. This involves some responsibility for promoting the adoption of carefully evaluated new technologies in the communities where they will be used.

Any extension of the processes of laboratory and clinical inquiry is viewed by many natural scientists with special alarm. But the limit on such activities will not be set by traditional patterns. We are bound to probe intently the array of outstanding practical questions in medicine and to determine anew which may be amenable to application of the scientific method. Where our techniques and skills will be useful, they should be dedicated to important utilitarian purposes. Where it is a waste to spend those skills, the case must be stated with candor, and other instruments supported. Implicit in this bargain is the dedication of resources sufficient to continue a healthy level of exploration without reference to immediate goals.

The trend toward public governance

The high cost of today's sophisticated and complex research requires science to stand in the queue for public support. More troubling still to scientists and public alike is the increase in the power of science to create real or imaginable threats to man and his planet.

Atomic physics began its sobering experience thirty years ago. Today's biologists are undergoing their trial in the discoveries that led to self-examination at Asilomar and to what this exercise in prudence set in motion. These are preeminently modern discomforts. No danger to environment or exchequer was laid to Newton; no one worried that Maxwell's "demon" was not kept in P4 containment. Even the Copernican "heresies" went unprosecuted for a century.

But the speculative hazards of plasmid engineering, like the real mutational power of radionuclides or the duplicity of DDT or Kepone, create dilemmas of serious proportions. The right to experiment with such things, whether at the laboratory bench or in ecological niches, is subject to social restrictions. The overriding principle is "First, do no harm!"

One night in December 1976, several colleagues and I sat about a conference telephone in Bethesda. From the box emerged the voices of members of the Experimental Biology Advisory Committee of the City of Cambridge, Massachusetts. To the questions of this group of concerned citizens, who, I imagine, were hovering over *their* telephone box, went back the best answers we could give. The subjects ranged from esoterica of molecular biology through practical details of the recently issued N.I.H. Guidelines for recombinant DNA research. This complex subject has been treated to much theater, distortion in the press, and irrationality in debate. Our conversation with the Cambridge Committee, however, clearly demonstrates that society, whose right to know is incontestable and whose need to understand is real, is intent upon achieving the essential communication.

For diverse reasons, then, and in numerous ways, the public governance of science is growing. I suspect it will continue to increase. With each step, we approach the critical limits to the external control of the scientific process. If these are exceeded, the system will falter and the promise will fail. How can we avoid a fatal encroachment? What are the conditions for entente between objective knowledge and value judgments in the complex society of imperfect men? There are few if any scientific facts that are pertinent to the resolution of these questions, but let me comment on several elements in the answer.

The sovereignty of science

I believe that it is most important to lay to rest the argument for the absolute sovereignty of science. Sometimes scientists in anger or frustration equate "intellectual freedom" with an absolute power on their part to determine the nature of all their experiments. This is a misreading of the first amendment to the Constitution and a denial of the complexity of modern society. Science has always been, and continues to be, firmly anchored in society's political, cultural, and other rules. It must operate in accordance with the law and cannot be above the law.

Historically, and often regrettably, the autonomy of science has been limited by the power of certain mores or taboos. Hans Morganthau points out that the social sciences have been the most restricted, for these impact directly on beliefs and social values.⁵ The 94th Congress's severe criticism of the National Science Foundation for some of its projects in the educational area bears witness to this. The natural sciences are less bedeviled by taboos, partly because their content is less subjective, partly because it is less understandable. Still, as I have indicated, the natural sciences are not immune.

Excessive social or political interference with science contains the seed of disaster for a nation and for man. There is serious danger in any intrusion, not clearly required for public safety, upon the processes of inquiry. I add also that there is grave peril in lay determination of what constitutes true achievement through use of the scientific method. Scientists must perforce choose their own heroes and ascertain what is scientifically valid. When they are wrong, the method contains its own corrective. The late Trofim Lysenko left as his legacy a melancholy gap in his country's scientific productivity and a disgraceful blotch on the ethic of knowledge. Similarly the macabre and meaningless experiments of physicians in thrall to Nazi tyranny are reminders that excessive statism in science is a modern possibility and a curse.

When scientists speak of "intellectual freedom" or "sovereignty of inquiry," not as innate rights but as abstractions intended to convey the essence of a process that must be self-directed, then their claims should be heard. The drives that promote skepticism and compel exhaustive experimentation, that permit intellectual leaps joining widely separate observations, and that fix an individual's attention to a narrow and often invisible target, are compounded of human qualities that cannot be enhanced by legislation. The creative engines can be fueled by governments, but they cannot be ignited by them. The

unknown cannot be programmed. Discovery cannot be scheduled—or even bought, except by indirection.

The morality in science that condemns the confusing of objective proofs with value judgments promotes unavoidable tension for scientists forced to accommodate to the social imperatives we have been considering. The external governors and lay patrons of research must tolerate these virtues of science and force no harm upon the internal ethic that is its strength.

The institutions that govern science

The scientific community, also, must tolerate and understand the nature of the political and legal institutions that govern science. The political institutions cannot precisely represent all interests of the public. Nor can the law speak with absolute certainty. Chief Justice Burger has written that law is inherently restraint, and that science must function within its framework.⁶ In his view, science is a great servant but a terrible master. Thus, our political institutions have reacted to the power of science by seeking control through law. William Pitt's declaration, "Where law ends, tyranny begins," is well known.⁷ But as Kenneth Davis explains, in *Discretionary Justice*, where law ends, discretion begins—and the exercise of discretion may mean either beneficence or tyranny, justice or injustice, reasonableness or arbitrariness.⁸

Davis is here considering the roles and responsibilities of government officials in decision-making, but the model is an apt one for decision-making in the scientific community. The deeper question is how to legislate and regulate with sufficient wisdom to allow for creative discretion. An extravagant use of government rules and regulations is no less threatening than an extravagant degree of scientific autonomy permitting arbitrary and capricious experimentation. Aristotle's principle that the rule of law is preferable to that of any individual is undeniable, but it does not mean that more laws and regulations will necessarily ensure more justice—either for the scientist or for the public.

To the ascending power of science, our political and legal institutions have responded with ever more complex restraints. Thus, we see limits being set by Congress, rules and regulations being fashioned by the Executive, and scientific decisions being reviewed by the courts.

Here the courts have both great power and enormous limitations. The laws of man, as enacted, implemented, and interpreted, are not subject to the same proofs as the laws of nature. The prime purpose of

the judicial process is to assure equity in reaching decisions. The courtroom is a retort for distilling values from facts, but its method for discovery is different from that of science. No test of Darwin's theory was involved in the famous legal debate of Darrow and Bryan.

When future courts are called upon to adjudicate disputes over science and technology, they may not be expected to take the side of the Enlightenment or to oppose it. The manner in which the courts ensure fairness in decision-making contains instruction for a scientific community now more frequently called to public account. Each question of the adversary must be attended to; none can be summarily dismissed. The facts or assumptions underlying each decision must be displayed. What is known must be clearly revealed; what is unknown must be acknowledged.

The laws that govern science

Although it may be necessary to resort to the courts for action, it is obvious that public governance of science more certainly depends upon how the laws are made and the rules enforced. As with the financial support of biomedical research, most of the rule-making is federal in origin. But it is not exclusively so. Regardless of one's assessment of recent rulings by the City of Cambridge on recombinant DNA research, they nevertheless demonstrate a concept of local authority that will appear here and there again. The fact that nearly every governor in the fifty states emulates the President in having his or her own science advisor is also a sign of the times. A long tradition of plural jurisdictions in secular matters does not spare scientific affairs, and a renewed acquaintance between town and gown is more likely to foster mutual respect than to break an uneasy *détente*. The burden to communicate clearly is on the shoulders of the universities while the requirement to understand is shared.

The public governance of science emanates predominantly from the acts and attitudes of the Congress, on which are based the rules and regulations of the Executive. In its authorizations and appropriations, this body takes a more direct interest in the condition and direction of biomedical research than does the British Parliament, the German Bundesrat, or similar legislatures in other nations supporting research from state treasuries. When Congressional attention seems inappropriate or excessive, it is well to recall the benefits that have accrued to science from this high interest of the lawmakers. Support has been generous and generally enlightened. It reflects appreciation that the greatest strengths of a people lie in brain-power as much as in fire-

power, and that the dependence of the economy upon advanced technology is nearly complete.

The problem of the Congress lies in its being a central terminus of petitioners for every form of favor and relief. Obligated to apportion resources for an ever-increasing list of social responsibilities, to hear from the charlatans as well as from the wise, to protect the minority and satisfy the majority, Congress goes about its impossible task by a series of accommodations. Intended or not, these involve decisions that reflect the legislators' attempts to reach a rough consensus on public priorities. The Budget Act,⁹ by which Congress has imposed funding limits upon itself, should tune more finely the mechanism for arriving at such a consensus.

Congressional control over scientific practices has emerged recently in actions intended to protect social interests, some parochial, some of very large proportions. For example, the Commission for the Protection of Human Subjects has been active since 1974. It was created by Congress¹⁰ out of concern for a full range of ethical issues in research, including the rights of the human fetus. This issue did not emerge from a scientific, but from a social controversy—the continuing debate over abortion. In 1975, H.E.W. regulations proscribed certain experiments on the products of abortion.¹¹ (Previously, Congress had limited federal support of research on abortifacients as a means of family planning.¹²)

In its concern to remove faulty medical devices from the marketplace, the Congress recently passed a law granting the Food and Drug Administration regulatory powers¹³ that parallel, and in some respects exceed, the agency's authority to regulate drugs. Another law, known as the Toxic Substances Control Act (TOSCA),¹⁴ became effective in 1977. It authorizes the Environmental Protection Agency to implement what may be the most sweeping legislation for the control of harmful effects of technology that has ever been enacted.

Further, Congressional actions not directed to the governance of science may impose upon it real or potential restrictions. Science, being government business, can get caught incidentally in attempts to reform other practices. Often the reformers are perplexed to discover unintended effects of new laws; and often these are gleefully exploited by other interests, which compounds the difficulties of redress.

The Federal Advisory Committee Act¹⁵ is one example of Congressional action which may have an unintended effect upon science. This law opens meetings of federal advisory groups to the public. Its applicability to the peer review process used by N.I.H. for over three decades remains unsettled after several court decisions and Congress-

sional hearings. Unless amended, a threat, potentially crippling, remains to the feasibility of adequate review of research grant applications. A second law, the Freedom of Information Act,¹⁶ opens approved grant applications to all upon demand. This privilege is not necessarily inimical to appropriate surveillance of scientific activities. When extended, however, to the seizure of raw laboratory data—as has occurred—or to the publication of preliminary information from clinical trials—as is possible—the potential for harm is boundless. A balance must be struck between the public's right to know and the confidentiality required to ensure excellence in scientific review and experimental practice. To achieve that balance in clinical trials, consumers are now included on certain of the safety committees that oversee the conduct of the study, so that the necessity to preserve confidentiality of data can be served without compromising the public interest.

My brief review of these Congressional actions only partly conveys the legislative ferment on policies governing science. And in addition, there is extensive Congressional surveillance over renewing authorizations and in appropriating annual funds for biomedical research.

Congress is an appropriate forum for reaching conclusions on priorities, but is ill-equipped to decide the individual merits of research or to promulgate specific rules and regulations for science. It falls to the Executive to define the rules to implement Congressional policies. And there is mounting tension between the research agencies and the regulators on how best to fashion those rules. For example, the laws passed to regulate medical devices and toxic substances provide for an exception for certain aspects of laboratory research. What this entails has yet to be settled by those agencies upon which the legislation places primary responsibility. Not settled either is the division of labor between the regulatory and the research agencies. The resources of the latter will likely be taxed to meet the laws' requirements, and their own programs may be the target of regulation efforts. The balance between increased regulations to protect the public and opportunities for research to promote the public health is becoming precarious.

I serve nowadays as chairman of an intergovernmental committee whose purpose is to accomplish extension of the N.I.H. Guidelines on recombinant DNA research to all laboratories across the land. It is possible that this narrow set of scientific techniques may never produce the prodigious benefits or hazards projected for it. Yet the exercise of synthesizing urgent public and private interests into workable controls is of no small importance. The participants seek a model applicable to the generic problems of governing experimentation with potentially dangerous things. The hybridization of scientific and social processes

may produce recombinants as troublesome as those of plasmid engineering; some guidelines are needed for *their* containment as well.

Standards, review, administration

The proliferation of federal regulations, and of new agencies to structure, define, and enforce them, is viewed by many as threatening individual initiative and other American traditions. These objections usually arise from industrial, trade, or professional quarters. Science to date has experienced, and survived, regulation of radiation sources, human experimentation, and hazards in laboratory workplaces. One would have to say that science generally has benefited from these controls. In so large and diverse a land, a reasonable set of common standards is reassuring to all concerned.

For this purpose, the federal regulatory agency has advantages that are self-evident. The federal regulation of experimental practices, however—like governance of many other things—must acknowledge an important principle: total faith in external regulation is dangerous illusion. Perhaps for science particularly, public control is critically dependent upon a complementary self-regulation by individuals and their institutions.

Responsibility for standard-setting, a necessary antecedent to any regulatory process, must remain largely in the hands of technical experts. The public must not be deluded that technical issues are better first addressed by laymen in courts, commissions, or hearing rooms. The subject matter is complex and in constant flux. Those engaged at the cutting edge must have first responsibility for the substance of standards, as in deciding what is excellent and safe and what is not. These critical decisions can be reached through central structures designed to elicit the best collective judgment. Further, there must be mechanisms to ensure fair consideration of non-technical concerns and values. Appropriate structures to serve these purposes must be in place and functioning credibly and openly. Effective means for providing for both technical and value judgments are exemplified by the N.I.H. peer review system, which has served science and the public well for thirty years. Its strength is that it operates on the ethic of knowledge—an orthodoxy of skepticism and prudence, a system of evidence and reasonable proof. At the initial level, it is a collective of technical experts operating centrally. At the next level, both scientists and laymen make recommendations on the relative values of proposed activities. The value judgments which they do not supply—for example, broad program priorities—are imposed later from public sources.

But the experts are a wellspring of initial, informed opinion that is irreplaceable.

Despite the strength of science's internal ethic, the real control of scientific practices cannot be exercised centrally, either by scientific peers at a distance or by commissions of mixed representation. Least of all can this be done by inspectors or enforcers of an external agency. It is "proximal governance"—that carried out between scientists and their home institutions—upon which society is most dependent. This is the level at which capabilities, observance of standards, and the responsibility shown by scientists for their co-workers, environment, and community are best monitored. Scientists must, and do, apply moral and ethical principles in the conduct of their research. But they are fallible. Like other people, they are at their best in a situation that makes them fully accountable to their peers. These, acting collectively, must take responsibility for all practices within their institution that bear upon the interests of the surrounding community and society at large.

N.I.H., in translating certain mandates for governance to the proximal level, has required the formation of review boards to oversee human experimentation, animal care, and now genetic recombination experiments. Other potentially hazardous work will doubtless have to be overseen in a similar fashion. Onerous as these responsibilities may be, they are meaningful and inescapable adjustments to the rising concern for public governance of science.

Summary

Some scientists will view the advent of more public governance as evidence that science has passed through its Periclean Age and is in decline. I remind them of Toynbee's comments on the disintegration of the fountainhead of Hellenic society.¹⁷ The failure of Athens, he said, was one of lost initiative. In its dream of sovereignty, the elite and creative city ignored the political and economic dictates of the changing civilization of which it was a part. The nemesis of creative institutions, Toynbee implies, is the temptation to idolize themselves to the point of failure to accommodate to altered realities. Thus, the isolation of Athens had to end, but its brilliance could have survived.

So it must be true of biomedical science emerging from a more sheltered period. The shift toward public governance does not spell the end of rationalism and scientific optimism—not if the instruments of government receive from the scientific community the full measure of cooperation upon which they desperately depend. Science must antici-

pate public needs or fears, learn better to explain, and extend interest in and responsibility for its technology beyond what has been traditional. No law, inspection force, or other external regulation can protect the public interest like responsible and responsive self-governance. Our example must prove our credibility. Scientific advice must be freely available to governments in thorough and understandable form. The wisest and most gifted must not be reticent in speaking. When they remain silent, the self-serving and less competent are ever ready to take their place.

The public, for its part, has no less a responsibility to understand the perishability of the capital, both human and physical, assembled by a nation's heavy investment in research. It must understand the organic nature of scientific processes and the ease with which they can be stifled by inflexible regulation or commands for discovery.

The interests of the public and of its scientific component can be served jointly. Indeed, they must be served together if our earthly presence is to survive. Ways will be found. Adversary processes need not imply totally adverse interests. Man's genius for discovery is matched by his art in compromise. As Frankfurter wrote, what ties people in friendship is not identity of opinions but harmony of aims.¹⁸

References

1. Derived by Division of Resources Analysis, Office of Program Planning and Evaluation, N.I.H., from data maintained by the National Academy of Sciences and the Association of American Medical Colleges.
2. Descartes, R. From *The Great Books of the Western World*. Encyclopaedia Britannica, Inc., Chicago, William Benton, 1952.
3. Bacon, F. From *The Harvard Classics*. New York, Collier, 1969.
4. Monod, J. *Chance and Necessity*. New York, Vintage Press, 1972.
5. Morgenthau, H. J. *Scientific Man vs. Power Politics*. Chicago, University of Chicago Press, 1946.
6. Burger, W. E. Reflections on law and experimental medicine. *UCLA Law Review* 15:436, 441, 1968.
7. Pitt, W. Speech on the Wilkes case, cited by Davis, K. C. *Discretionary Justice, A Preliminary Inquiry*. Urbana, University of Illinois Press, 1971, p. 3.
8. Davis, K. C. *Ibid.*
9. P.L. 93-344.
10. P.L. 93-348.
11. 45 CFR Part 46.
12. P.L. 91-572.
13. P.L. 94-295.
14. P.L. 94-469.
15. P.L. 92-463.
16. 5 USC 552.
17. Toynbee, A. J. *A Study of History*. New York, Oxford University Press, 1947.
18. Frankfurter, F. Personal communication to David L. Bazelon, 1959.

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